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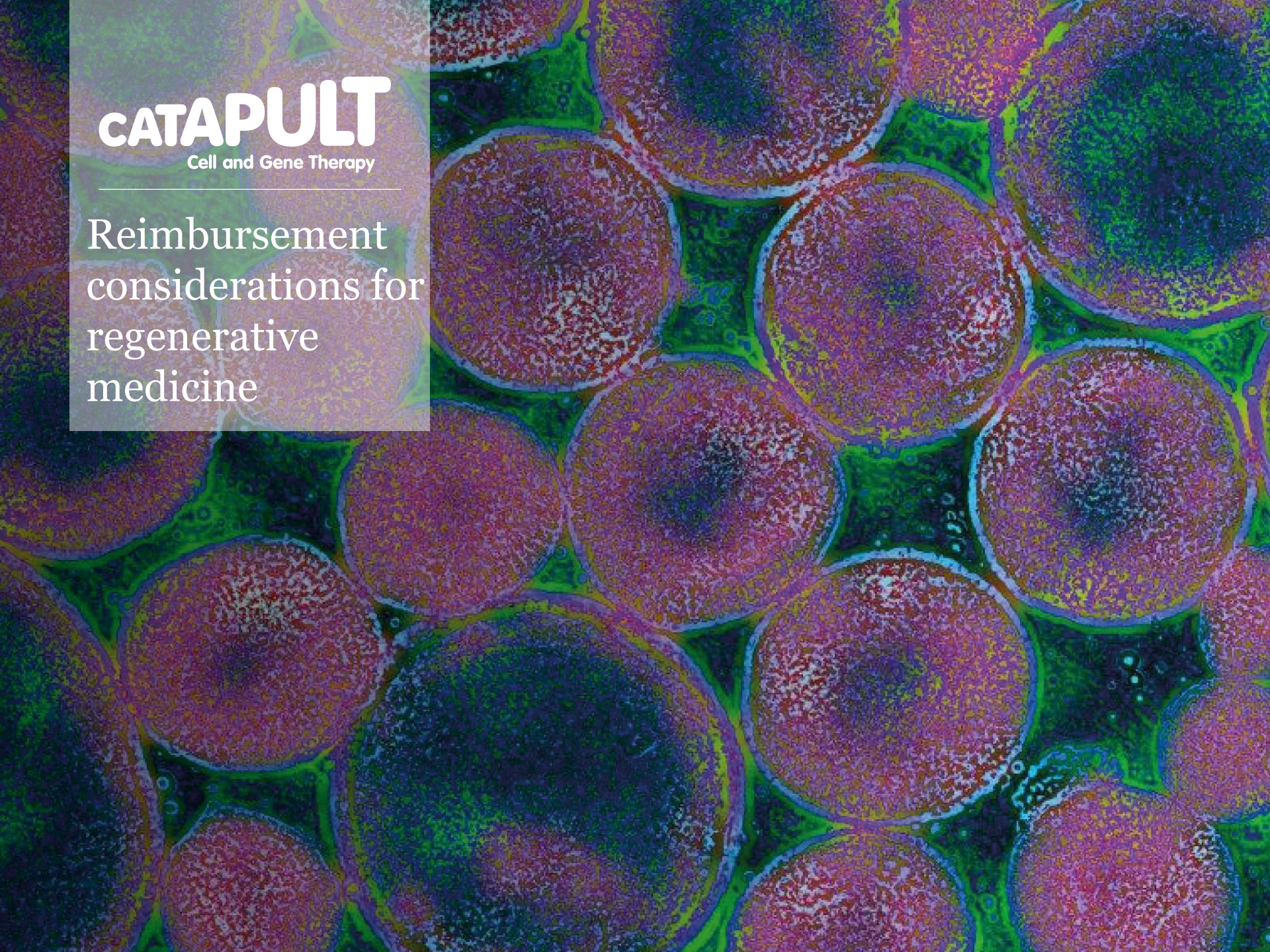
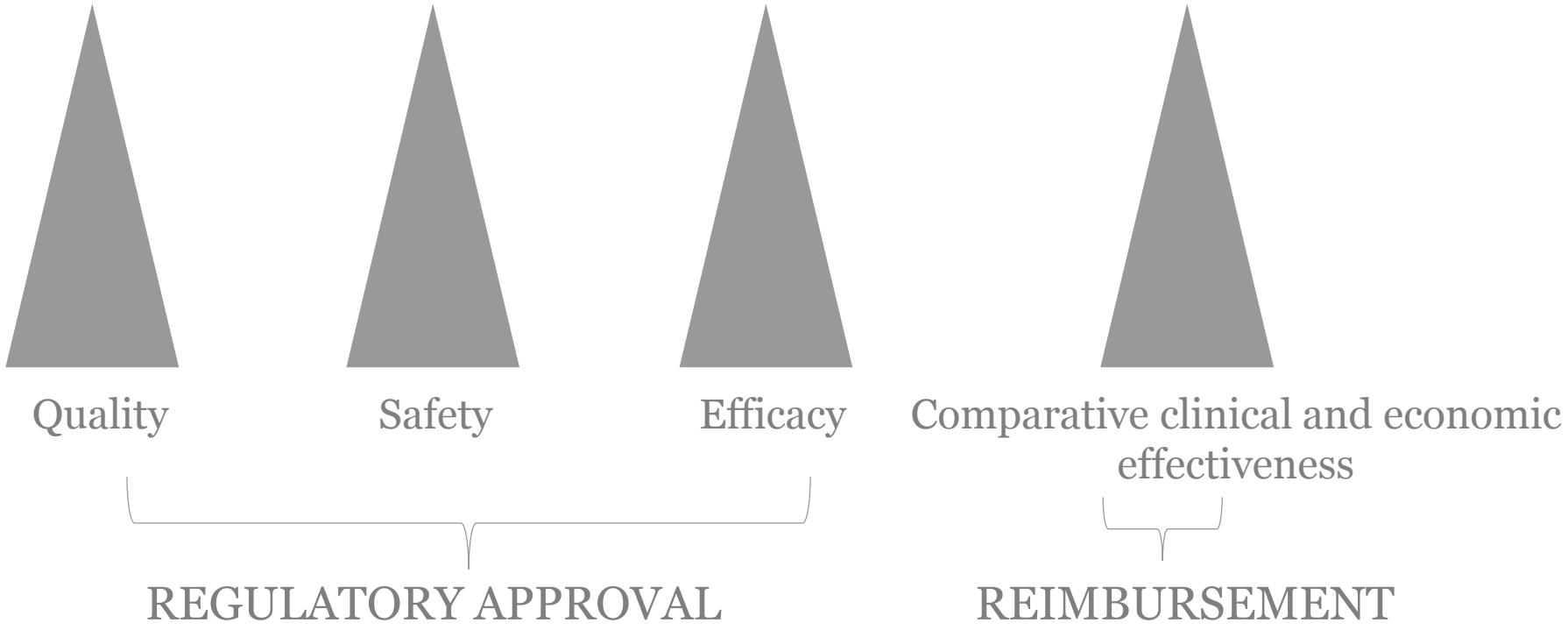
Reimbursement considerations for regenerative medicine



There are differences in data requirements between EMA approval and reimbursement assessments; the latter require evidence of comparative effectiveness vs SOC*



*SOC: Standard-of-Care

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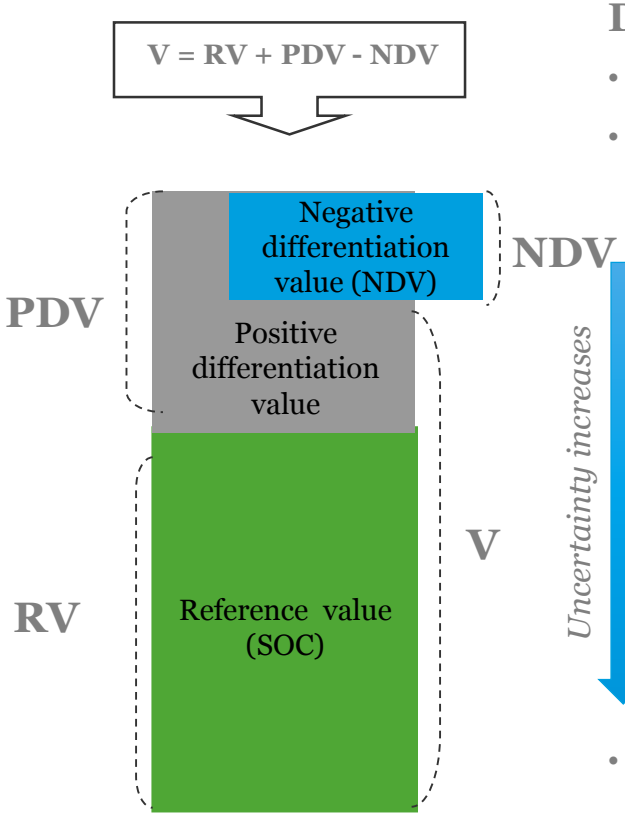
Reimbursed price for innovative therapies is subject to value-based assessments; these link price to the therapy's added-value

PRINCIPLES OF VALUE-BASED ASSESSMENTS



Differentiating value

- Added-value defined in terms of clinical and economic terms
- Comparative data against the SOC/BSC **per country** is required:
  - Gold-standard: H2H RCT
  - Indirect comparisons may be leveraged
  - Meaningful comparative data from single arm trials can only be generated if:
    - Quality historical control data is available
    - Natural history of disease is well known
    - Patient population homogenous
  - Modelled data may be acceptable in certain markets
    - e.g. Extrapolations in the UK
- For a given indication, "V" varies depending on therapeutic positioning

If no comparable treatment and measures of outcome are available, manufacturers must work with KOLs to develop appropriate measures

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Various approaches are used to translate differentiating value to reimbursed price (depending on geography)

Some frequently applied approaches include:

- Budget impact analysis
- Cost-effectiveness analysis
- International price referencing

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Budget impact (BI) assessments are commonly used by payers to quantify the economic impact of introducing a novel therapy

Key drivers:

- Change in costs per patient from displacing existing therapies

(usually healthcare budget only)

- Number of patients treated
- Time horizon (≤5 years)

BUDGET IMPACT	
Total Population of England	*50,542,505*
Target population p.a.	*1,000*
SOC price per patient	*£5,000*
New Therapy price per patient	*£6,000*
Probability of rehospitalisation with SOC	*2.00%*
Probability of rehospitalisation with New Therapy	*1.00%*
Cost per rehospitalisation	*£20,000*

Illustrative exemplar of a novel budget neutral therapy

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Market share of New Therapy	0%	20%	40%	60%	80%	100%
SOC Costs	£5,000,000	£4,000,000	£3,000,000	£2,000,000	£1,000,000	£0
New Therapy Costs	£0	£1,200,000	£2,400,000	£3,600,000	£4,800,000	£6,000,000
Total Drug Costs	£5,000,000	£5,200,000	£5,400,000	£5,600,000	£5,800,000	£6,000,000
Rehospitalizations Avoided	0	10	20	30	40	50
Reduction in Rehospitalization Costs	0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Costs						
Change in Drug Costs	£0	£200,000	£400,000	£600,000	£800,000	£1,000,000
Change in Rehospitalization Costs	£0	-£200,000	-£400,000	-£600,000	-£800,000	-£1,000,000
Total Change in Costs	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**

In England the £20M annual net BI threshold over first 3 years post-launch informs price and volume potential

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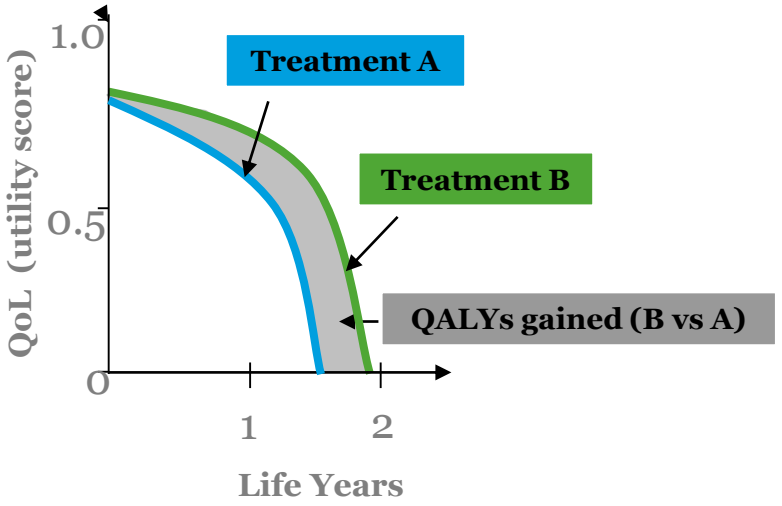
In certain markets (e.g. UK, Canada, Australia, Nordic, Netherlands) the cost-utility framework is used to inform reimbursed price potential

$$\text{ICER} = \frac{\text{Cost B} - \text{Cost A}}{\text{QALY B} - \text{QALY A}}$$

QALY = Life expectancy *(life years)* x Quality of life *(utility)*



- The ICER informs price potential
- UK ICER thresholds:
  - ≥500 patients: £20-30K (~50K CAD)
    - For end-of-life up to £50K
  - For very rare conditions: ICER up to £300K (depending on magnitude of QALY gain)

Unlike BI, CU has greater potential in capturing the full benefits of RegenMed

- It rewards for gains in life years and QoL

- It covers a longer horizon (e.g. lifetime for chronic disease)

- Can accommodate modelled data e.g. extrapolations to support long term claims

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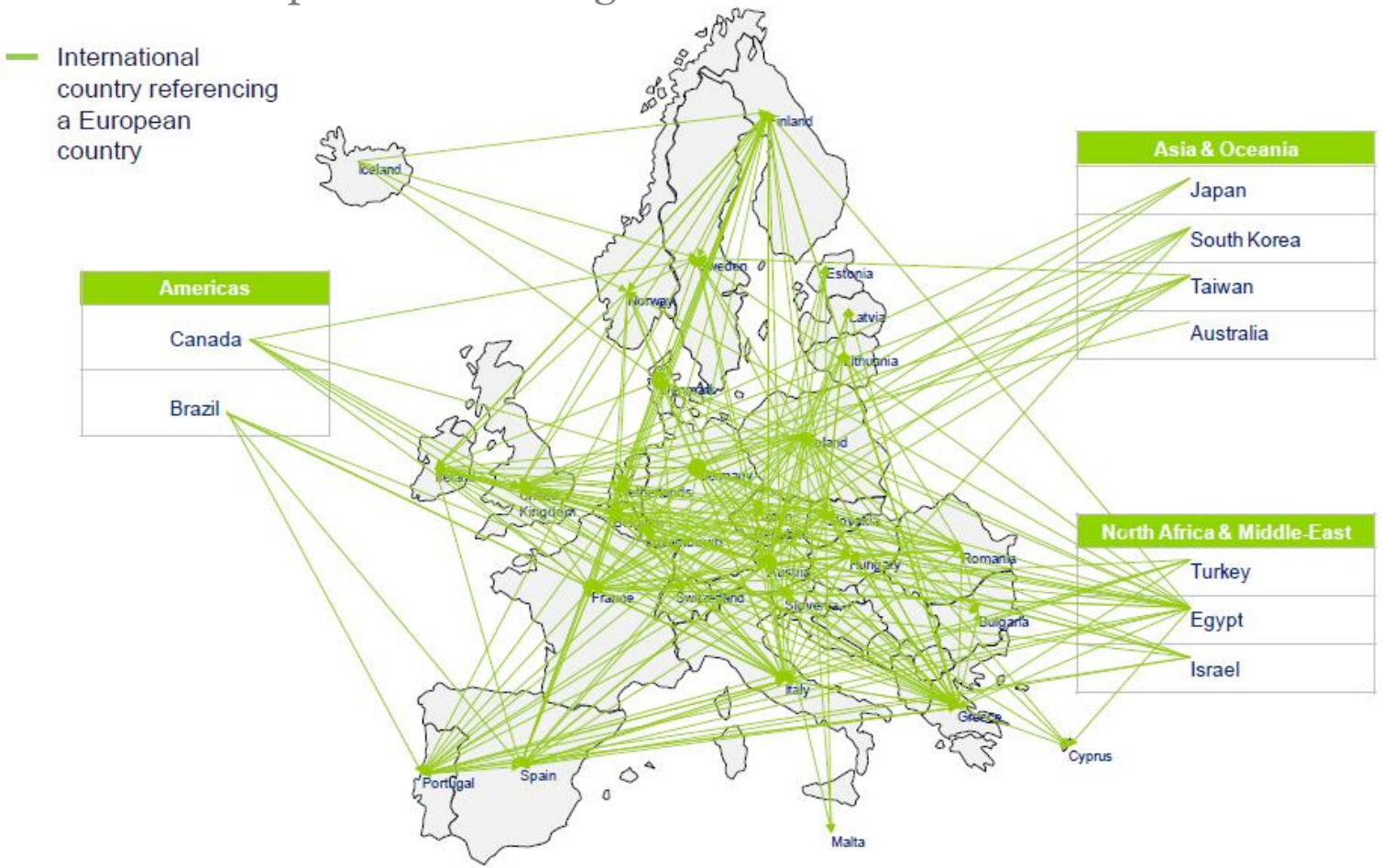
Often price assessments in one country are influenced by price decisions in others

International price referencing



Source: Deloitte, Model N, Professional Pricing Society Webinar

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How differentiating value is translated to reimbursed price varies by geography: BIG 5 EU EXEMPLAR

Most commonly used levers by market

Levers	UK	France	Germany	Italy & Spain
1st order	Comparative clinical effectiveness of the novel therapy vs a relevant comparator in the given market			
2nd order	Cost-utility Net Budget Impact threshold of £20M p.a.	*ASMR1-3:* International price referencing (EU4) + Cost-utility *ASMR4-5:* Domestic comparator price Price-volume agreements	*With added benefit:* Premium over the comparator Efficiency Frontier International price referencing (EU15) *No added benefit:* Domestic comparator price	*With added benefit:* Premium over the comparator + Budget Impact + International price referencing (cost-utility: minor lever) *No added benefit:* Domestic comparator price

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Common challenges with ATMP supporting data at launch impacting reimbursement negotiations

- Limited comparative effectiveness data against SOC/BSC due to:
  - Unavailability of H2H comparative data
  - Randomised placebo controlled trials may not be feasible in certain cases
    - Limits prospect for credible 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
- Short-term data at launch
  - Uncertainty on maintenance of effect especially when value proposition is around long-term claims
  - Uncertainty on long-term safety
- Statistical significance can be limited by small sample sizes
- Surrogate rather than hard clinical outcomes
  - Magnitude of effect may be overestimated (*NICE Regenerative Medicine Study, 2016*)

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Learning from the cell and gene-based cancer immunotherapies assessed by NICE so far

Therapy	Data uncertainty	Decision
Sipuleucel-T (For asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated)	Due to limitations with indirect comparison against lower cost oral abiraterone, superiority and therefore cost-effectiveness could not be established	Not recommended
Talimogene laherparepvec (For unresectable, regionally or distantly metastatic {Stage IIIB, IIIC and IVM1a} melanoma that has not spread to internal organs)	A reliable estimate of its effectiveness compared with SOC (systemically administered immunotherapies) could not be established	Restricted use; recommended only when treatment with systemically administered immunotherapies is not suitable

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Four complementary approaches for dealing with data uncertainty (a UK perspective)

1. The "extrapolation process selection algorithm" by the Decision Support Unit of NICE on how survival data could be credibly extrapolated beyond trial duration
2. Using outputs from the cost-utility framework to quantify payer uncertainty; modulate price to reduce impact of uncertainty for the payer
3. Identify the managed entry agreement (MEA) that minimises uncertainty as per:
    i. *"Exploring the assessment and appraisal of regenerative medicines and cell therapy products", NICE, March 2016*
    ii. *"Framework for analysing risk in HTA and its application to MEAs", DSU, January 2016*
4. Conditional Reimbursement: The Cancer Drug Fund

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The "extrapolation process selection algorithm" by NICE DSU* guides how survival data can be extrapolated beyond the trial observation period

The need:

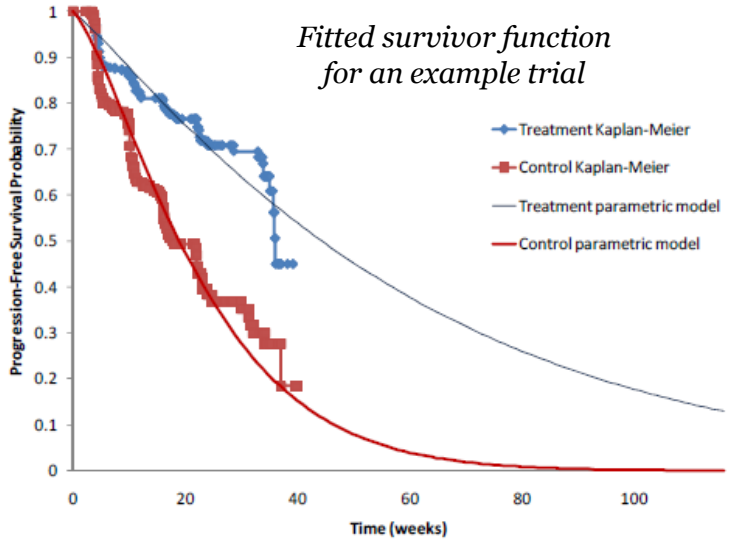
- According to the NICE TA framework, it is mean rather than median survival that needs to inform the lifetime horizon of the cost-utility analysis
  - However such data tend not to be available at launch
    - Therefore estimates of entire survival distributions are required

The objective:

- The "extrapolation process selection algorithm" guides on how to best address the evidence gap through credible extrapolations

The process:

- Fitting and testing a range of survival models (regression frameworks) based on:
  - Internal validity (how well they fit to the observed data)
  - External validity (how plausible the extrapolated portions are)



*NICE Decision Support Unit Technical Support Document 14: *Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data, March 2013*

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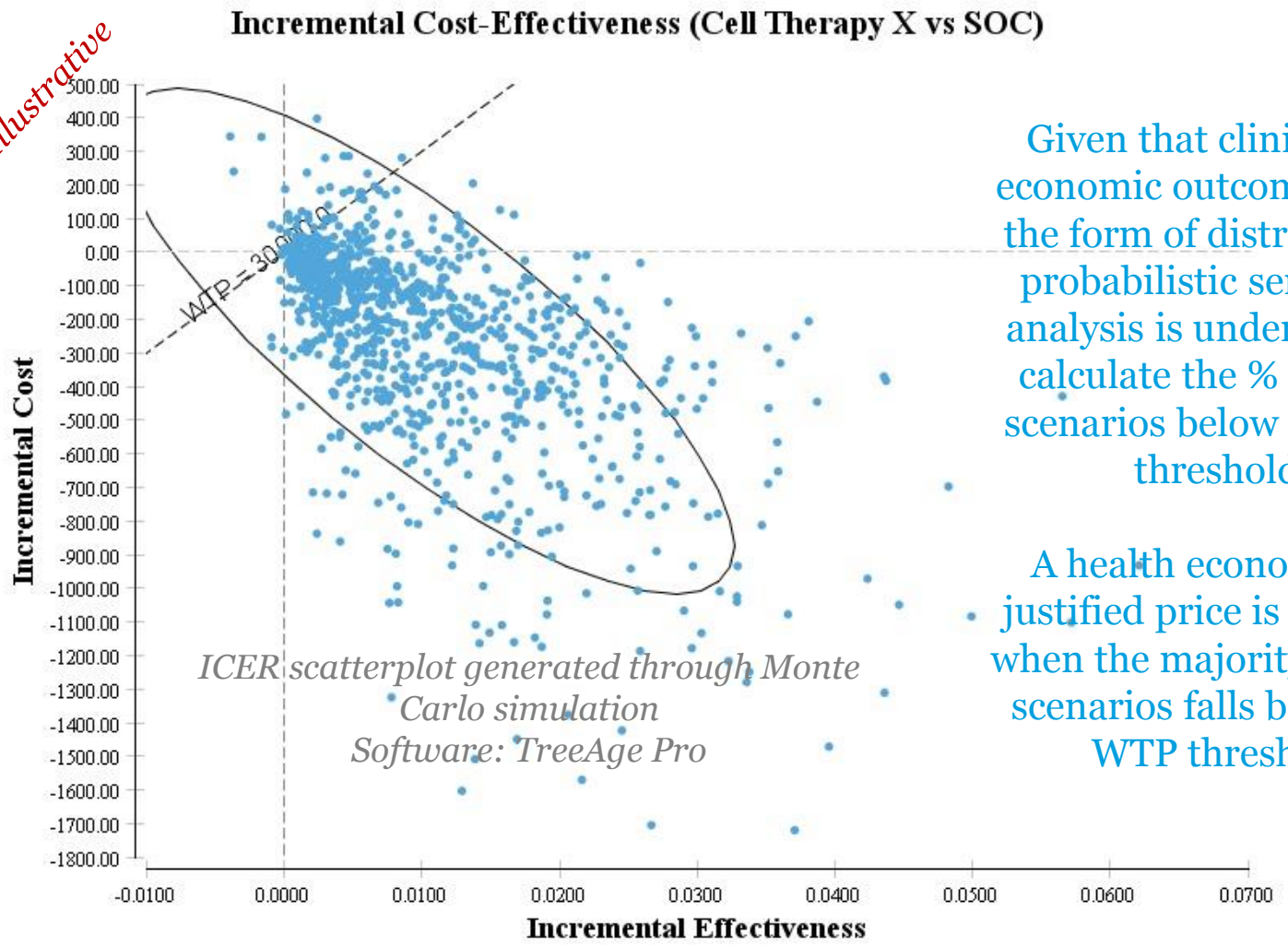
Using the cost-utility framework, impact of data uncertainty on probability of being CE is quantifiable; price can then be modulated to minimise uncertainty



ICER scatterplot generated through Monte Carlo simulation
Software: TreeAge Pro

Given that clinical and economic outcomes are in the form of distributions, probabilistic sensitivity analysis is undertaken to calculate the % of ICER scenarios below the WTP threshold.

A health economically justified price is achieved when the majority of ICER scenarios falls below the WTP threshold

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Two other outputs from the cost-utility framework can be used to inform uncertainty

Output	Value
Incremental Net Health Effect (NHE) *(expressed in QALYs)*	*Incremental NHE =* *[(Incremental Effectiveness) x (ICER threshold)] –[Incremental Costs]* • Measures whether the additional QALY gain from a therapy is large enough to justify its additional cost (over the SOC) • Should be a positive value ○ The larger, the more likely the adoption
Consequences of decision uncertainty *(expressed in QALYs)*	• Measures the opportunity cost for the healthcare system if due to uncertainty, it adopts the less beneficial therapy • Should be much smaller than the Incremental NHE ○ The smaller the more likely the adoption

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The three uncertainty metrics can be used to identify appropriate Managed Entry Agreements (MEAs)

- MEA taxonomy: Price adjustments of various kinds (from straight discounts to performance based) with or without further evidence collection (RCTs, observational studies, further analysis of existing data)

Illustrative

Scenario	ICER	Incremental NHE QALY *	Probability Cost Effective	Consequences of decision uncertainty QALY *	Adoption potential
£100,000 one-off acquisition cost per patient	£50,000	-55	50%	300	Very low
10% discount	£45,000	200	65%	250	Low
Pay-for-performance: *payment only for patients with remission by day 30*	£40,000	250	70%	100	Possible
Lifetime leasing: *payment on a monthly basis as long as patient remains alive (£2,000 pcm)*	£35,000	1000	99.5%	2	High

Maximise *Minimise*

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

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I. Balancing opportunities and challenges with MEAs: enabling implementation

Areas of focus for performance-based MEAs:

Feasible approaches to short and long-term patient follow-up

Validated surrogates and/or hard outcomes to be measured

Timely data analysis and adjustment to payments based on performance at individual patient or cohort level

- E.g. The 60-day claim period for Velcade in MM was too tight resulting in missing claims

Timescales for reassessment of coverage decisions

Who is responsible for what: the role of the NHS, the manufacturer and/or third party organisations

- Resource implications for the NHS and manufacturer (costs, timescales)

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II. Balancing opportunities and challenges with MEAs: achieving win-win agreements between manufacturers and payers

Choosing between MEAs with similar effect on uncertainty

Performance-based example: Rebates vs Annuities

	Manufacturer		Payer	
	Pros	Cons	Pros	Cons
Rebates	Faster revenue generation	Large Budget Impact (BI) limits access*	Price reduction	Is there a reliable process to inform timely rebates? Admin. burden
Annuities	Small BI enables wider access	Slow revenue generation; is it commercially viable?	Reduced BI	Admin. burden

**Proposed £20M annual net BI threshold over first 3 years post-launch*

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The Cancer Drug Fund (CDF) and coverage with evidence development (effective as from July 2016)

- Oncology specific
- Following initial NICE review, when there is potential clinical benefit but uncertain cost-effectiveness, drug can be considered for funding within the CDF **for a time limited period**
- Funding is subject to company agreeing to:
  - A "commercial access arrangement" which is affordable within the available CDF budget
    - Price should result in an ICER ≤NICE threshold
  - Fund the collection of a pre-determined data set, during a period normally ≤24 months
    - At the end of this period, NICE will undertake a review and issue either a 'recommended' or 'not recommended' for routine use decision

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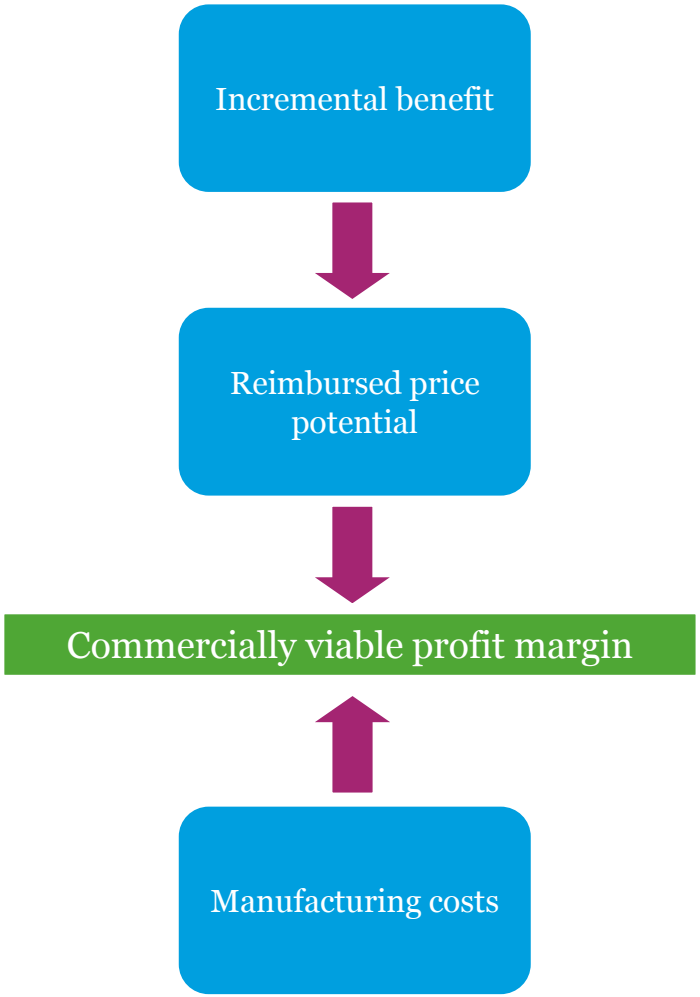
Paradigm shift: The considerably higher cost of RegenMed necessitates earlier consideration of reimbursement matters

Commercially viable profit margins are determined by manufacturing costs and reimbursed price

Reimbursed price is proportionate to:

- The magnitude of incremental benefit vs the SOC:
  - For the patient and the healthcare system
- The cost of the displaced therapy (SOC)
- For small molecules, lower manufacturing costs provide flexibility over commercially viable price thresholds
- Demonstration of statistically significant incremental clinical benefit ≥MID often suffices
- The considerably higher cost of RegenMed requires much greater incremental benefit
- Therefore commercial risks are higher
- Accounting for reimbursement considerations earlier and informing RegenMed R&D strategy accordingly, is of priority



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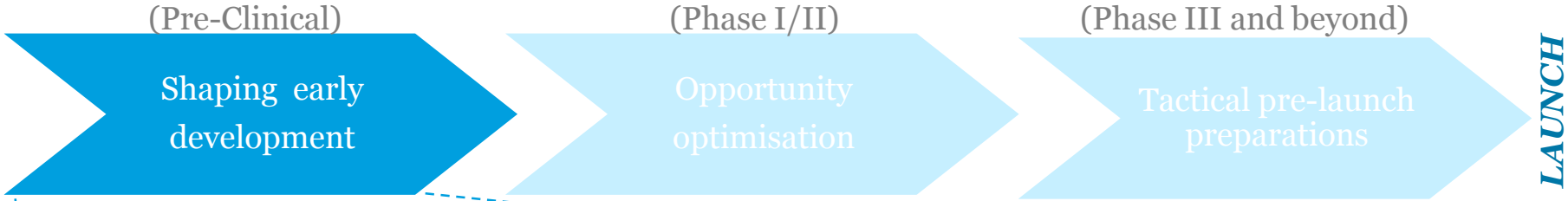
To secure commercial viability, robust value optimisation and market access strategies need to be developed; preparations should start prior to clinical development and continue in parallel

Our HE&MA deliverables across the key stages of development



Shape early development by identifying:

- Room for innovation
  - Value maximising indication and therapeutic positioning
    - In order to select optimal 1st/follow-up indication and therapeutic position(s)
- Key clinical and economic drivers of product value
  - In order to inform TPP
- Interrelationship between incremental benefit, reimbursed price, manufacturing costs and profit margins; in order to:
  - Define product performance and manufacturing cost thresholds for commercial viability
  - Inform clinical and manufacturing strategy
  - Define go: no go decision making criteria

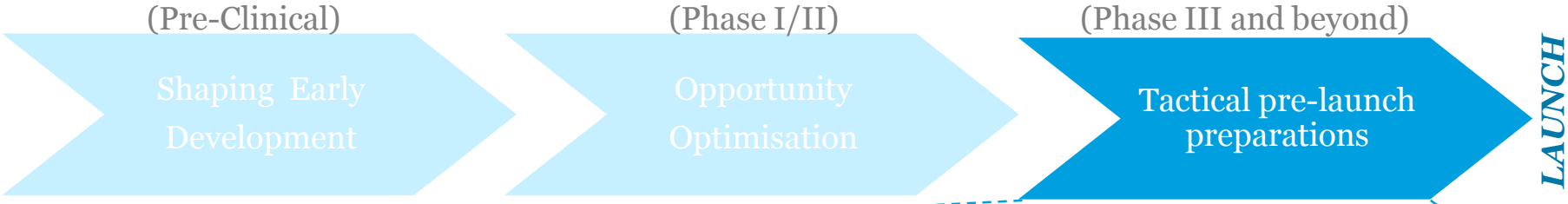
Subsequently market access stakeholder input should be sought to inform pricing and reimbursement strategy

Our HE&MA deliverables across the key stages of development

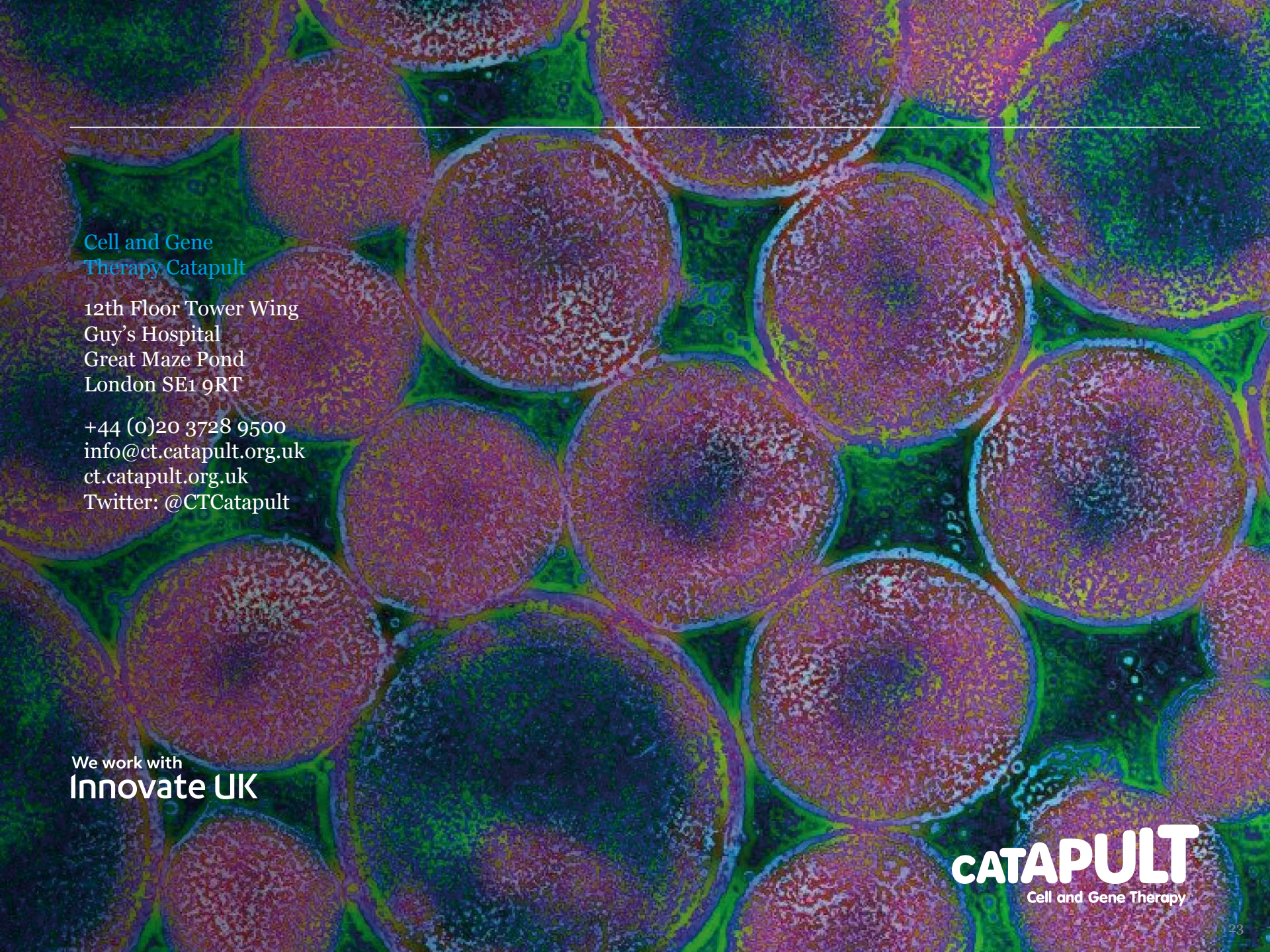
- Prior to embarking on pivotal trials, engage with key market access stakeholders in major healthcare markets to understand evidence requirements
  - National/ Regional / Local level payers
  - HTA bodies advising payers (e.g.NICE, SMC, HAS, G-BA, parallel EMA/HTA advice)
  - PPIs (Physician Payer Influencers)
- Development of early pricing & reimbursement strategy
  - "Value Story"
  - Clinical and economic evidence generation plan to support Value Story (RCT/observational/modelled data)
  - Vision on positioning, pricing & reimbursement potential
  - Account for differences in markets access drivers across major healthcare markets
  - Strategies to address market access hurdles

Development of contingency plans in preparation for launch is key, especially when data uncertainty is high

Our HE&MA deliverables across the key stages of development



- Finalise:
  - 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 contingency planning:
  - Risk-sharing schemes
    - Minimise uncertainty
    - Ensure implementability
    - Ensure commercial viability
  - Post-launch evidence generation plans



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