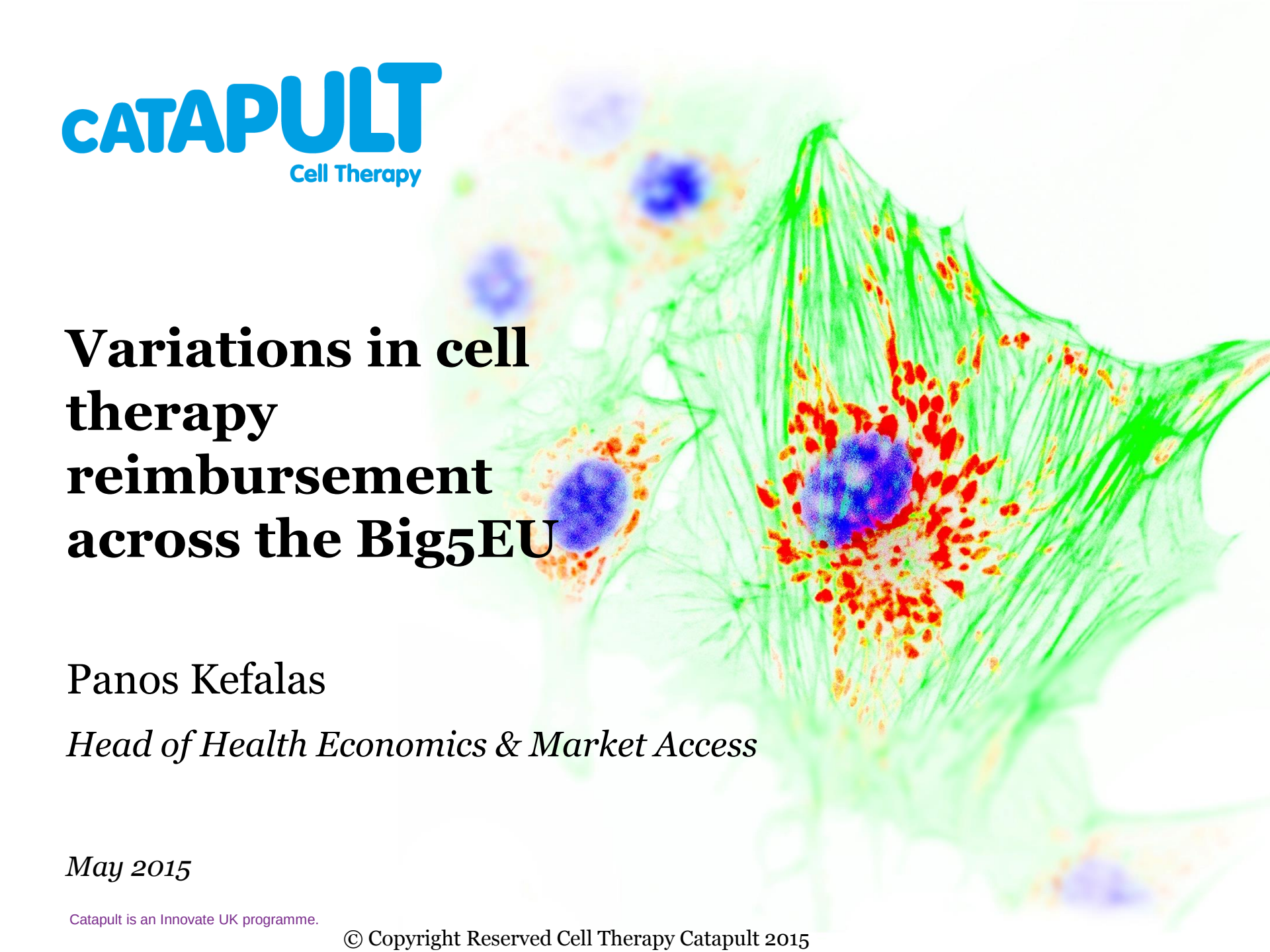
CATAPULT
Cell Therapy



Variations in cell therapy reimbursement across the Big5EU

Panos Kefalas

Head of Health Economics & Market Access

May 2015

Catapult is an Innovate UK programme.

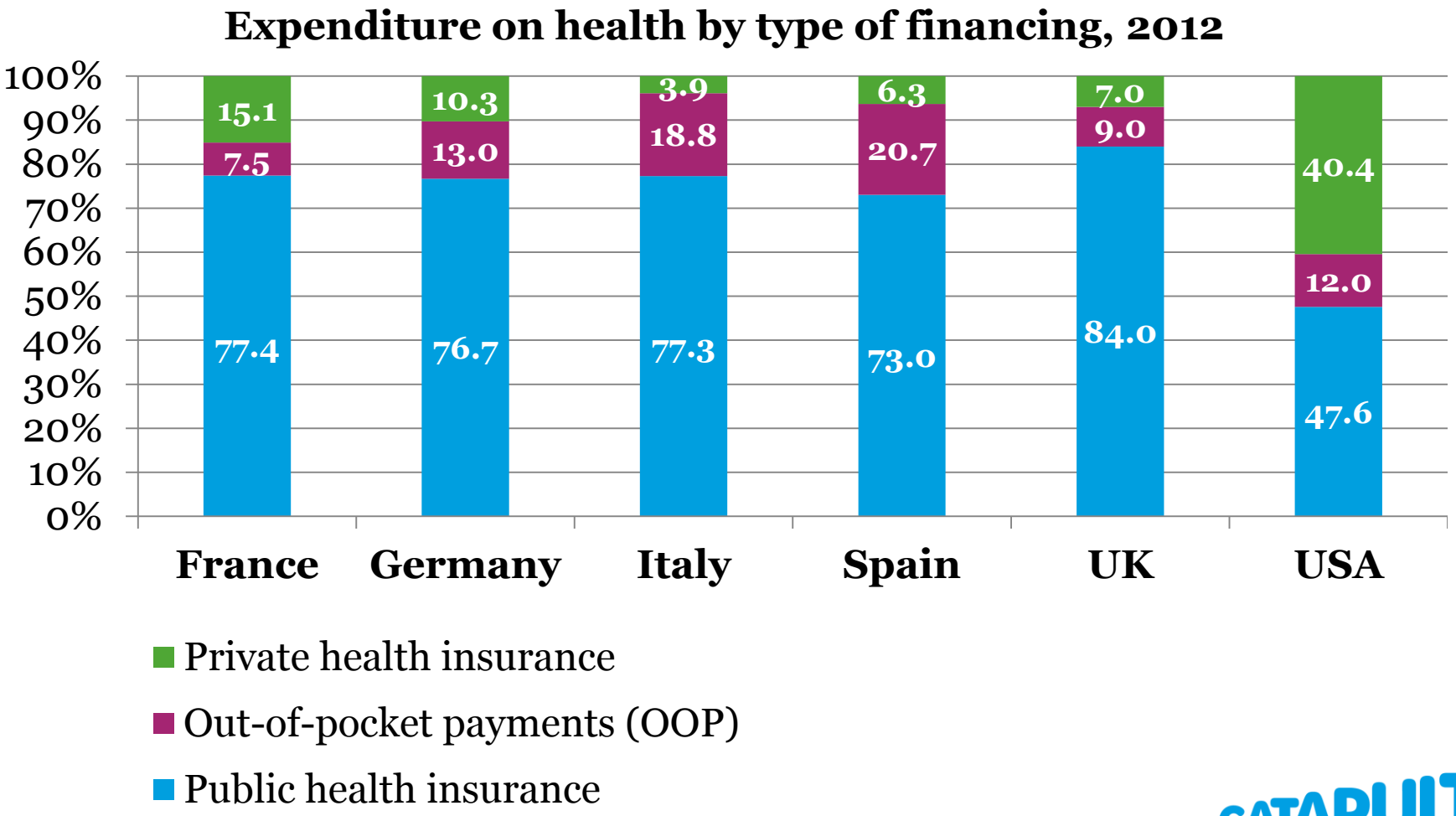
Presentation focus

- Variation in pricing and reimbursement (P&R) frameworks for cell-therapies by:
  - A. Geography across Big5EU (France, Germany, Italy, Spain and UK)

  - A. Therapy features:
    - magnitude of incremental benefit vs alternative therapeutic approaches
    - size of target population
    - regulatory status
- Scope:
  - Hospital setting (in- and out-patient)
  - The public payers

CATAPULT Cell Therapy

Unlike the US, the Big5EU healthcare expenditure is largely driven by public health insurance



Source: OECD Health Statistics 2014

CATAPULT Cell Therapy

In terms of formulary inclusion of innovative therapies, private insurance does not provide significant advantage over public

Country	Main features of private insurance

Germany	• Typically cover same treatments as public; added-value from:
	  ◦ shorter waiting time
	  ◦ greater choice of providers
	  ◦ access to private hospitals
	  ◦ UK: excludes chronic disease

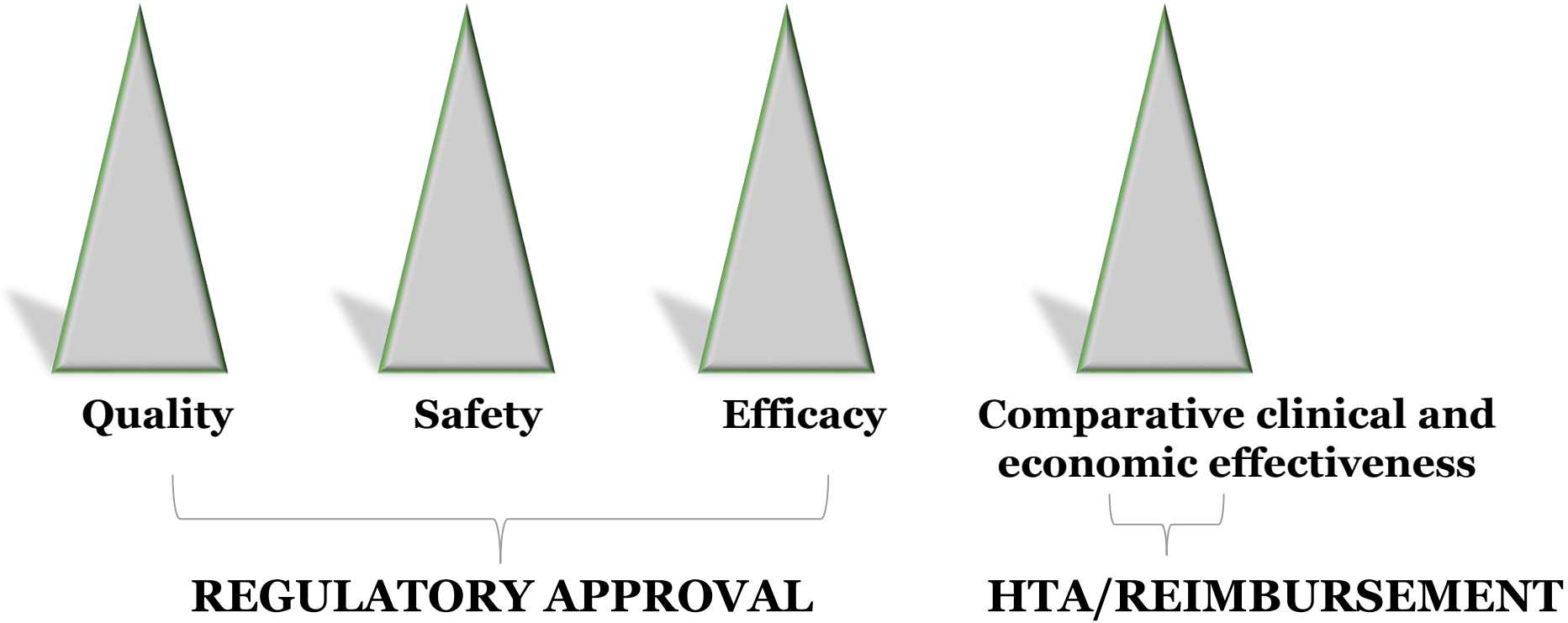
Italy	
Spain	
UK	
France	• Covers patient co-payments only • The non-profit insurers (Mutuelles) have little impact on P&R

The priority for cell therapies in Big5EU is to pursue public reimbursement

CATAPULT Cell Therapy

Licensed ATMP category

There are differences in data requirements between EMA approval and HTA across the Big5EU; the latter commands evidence of comparative effectiveness vs SOC/BSC

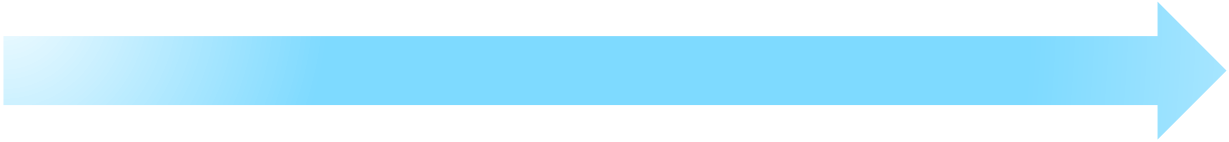


Insufficient comparative effectiveness evidence penalised ChondroCelect, MACI, Provenge

- Protracted MA negotiations
- Conditional or NO reimbursement

In Big5EU, the assessment of reimbursed price for innovative licensed therapies has shifted towards value-based models

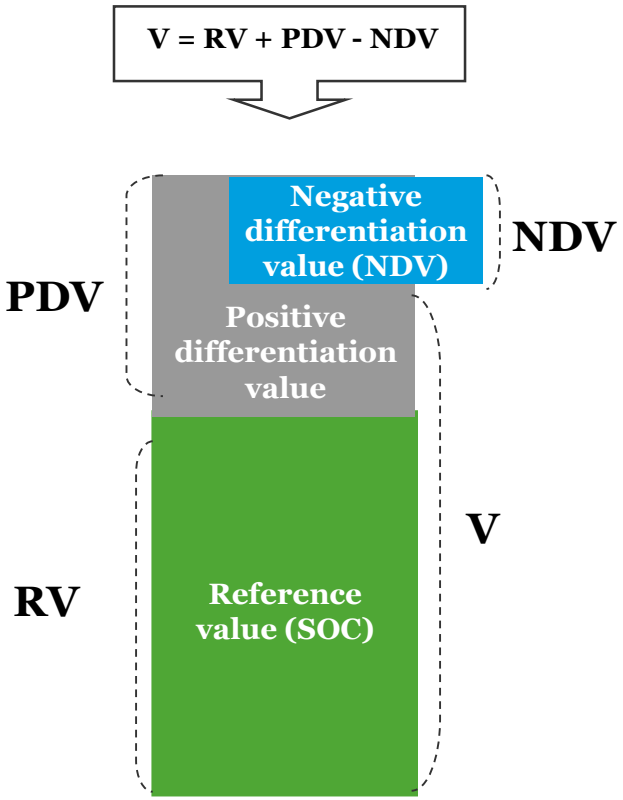
	Cost-based	Competitor-based	Value-based
What is it?	• Price based on costs, expected sales and margins	• Price driven by competition	• Price based on **<u>comparative effectiveness</u>**
Examples	• Cost-plus pricing	• Penetration pricing • Reference group pricing	• Cost-utility based pricing
Comments	• Becoming obsolete • *Exception:* unlicensed ATMPs	• Enforced for **undifferentiated** products	• Typical for **differentiated** products



CATAPULT Cell Therapy

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

PRINCIPLES OF VALUE-BASED ASSESSMENTS



Differentiating Value

- Includes:
  - Clinical effectiveness
  - Economic effectiveness: budget impact, cost-effectiveness, cost-consequence
- Comparative data against the SOC/BSC **per country** is required:
  - Gold-standard: H2H RCT
  - Indirect comparisons can be leveraged
  - Comparisons can be based on modelled data to address:
    - Trial imbalance (observational vs RCT)
    - Treatment switching/cross-over
    - Extrapolations
- For a given indication, "V" varies depending on therapeutic positioning

CATAPULT Cell Therapy

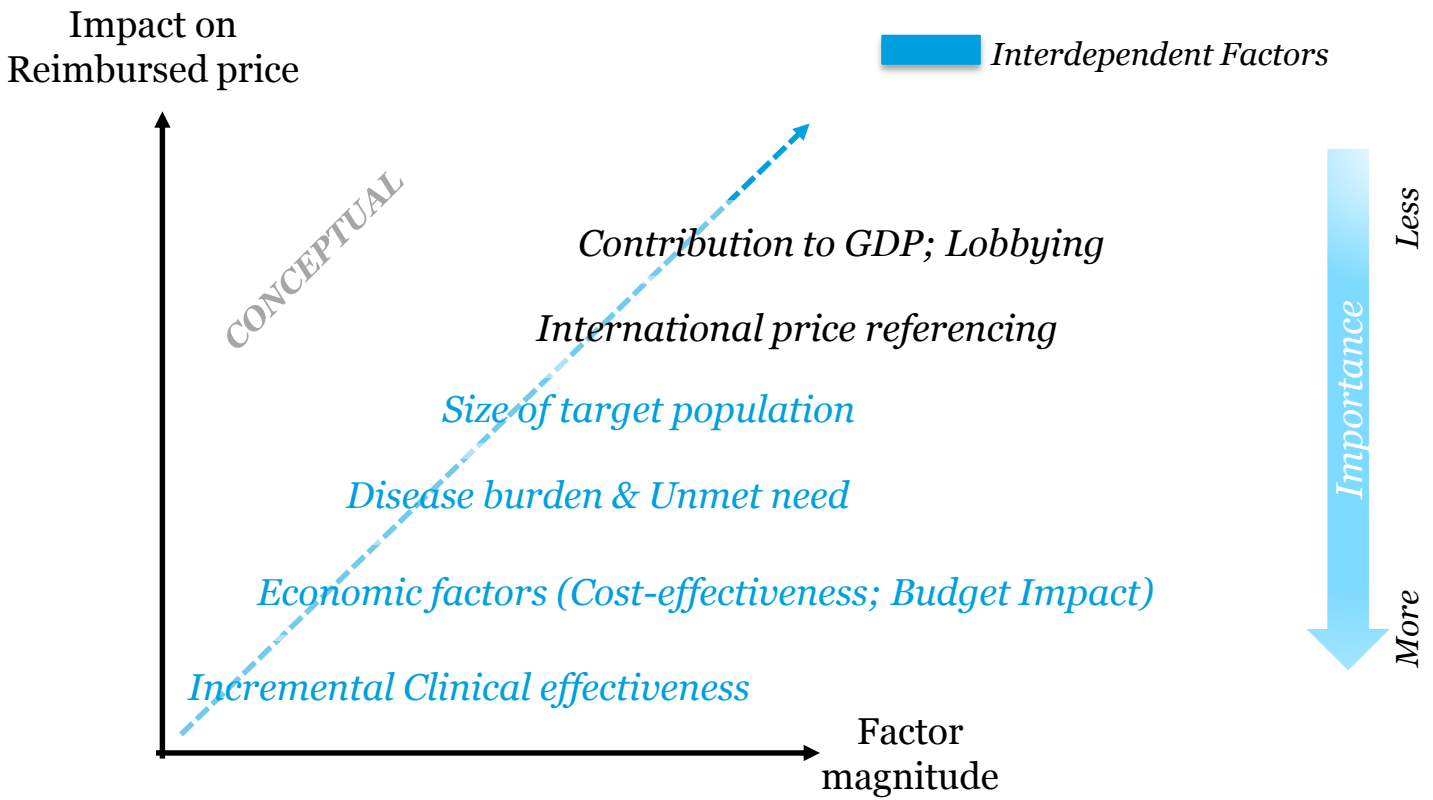
How differentiating value is captured and translated to reimbursed price varies by geography

Most commonly used levers by market

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

CATAPULT Cell Therapy

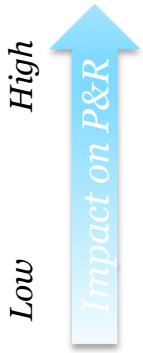
Additional factors impact willingness to pay and reimbursed price potential across the Big5EU



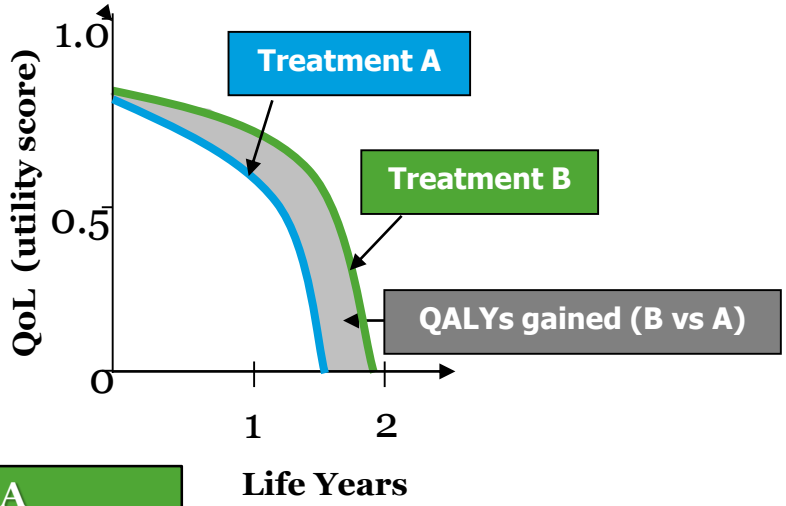
- Willingness to pay higher in very rare diseases & small subpopulations of larger indications
  - Due to budget impact and disease burden considerations
- Where significant economic constraints exist, P&R largely influenced by budget impact (BI)
  - This limits capacity to reward upfront for long-term benefits
    - Northern vs Southern Europe

Unlike BI, CUA and its reliance on modelled data provides an opportunity for cell therapies to capitalise on long-term benefit claims; however its application and impact vary across Big5EU

- Cost-utility analysis (CUA) applicable in:



  - UK
  - France: ASMR1-3
  - Spain
  - In Italy not mandatory
  - Germany: N.A



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

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

- The ICER is an indicator of price potential
- Explicit ICER thresholds only in UK
  - ≥500 patients: £20-30K
    - For end-of-life up to £50K
  - Very rare conditions: ICER less relevant
    - e.g. Cerezyme (Gaucher's / prevalence 270) commissioned: ICER =£391,244

CATAPULT Cell Therapy

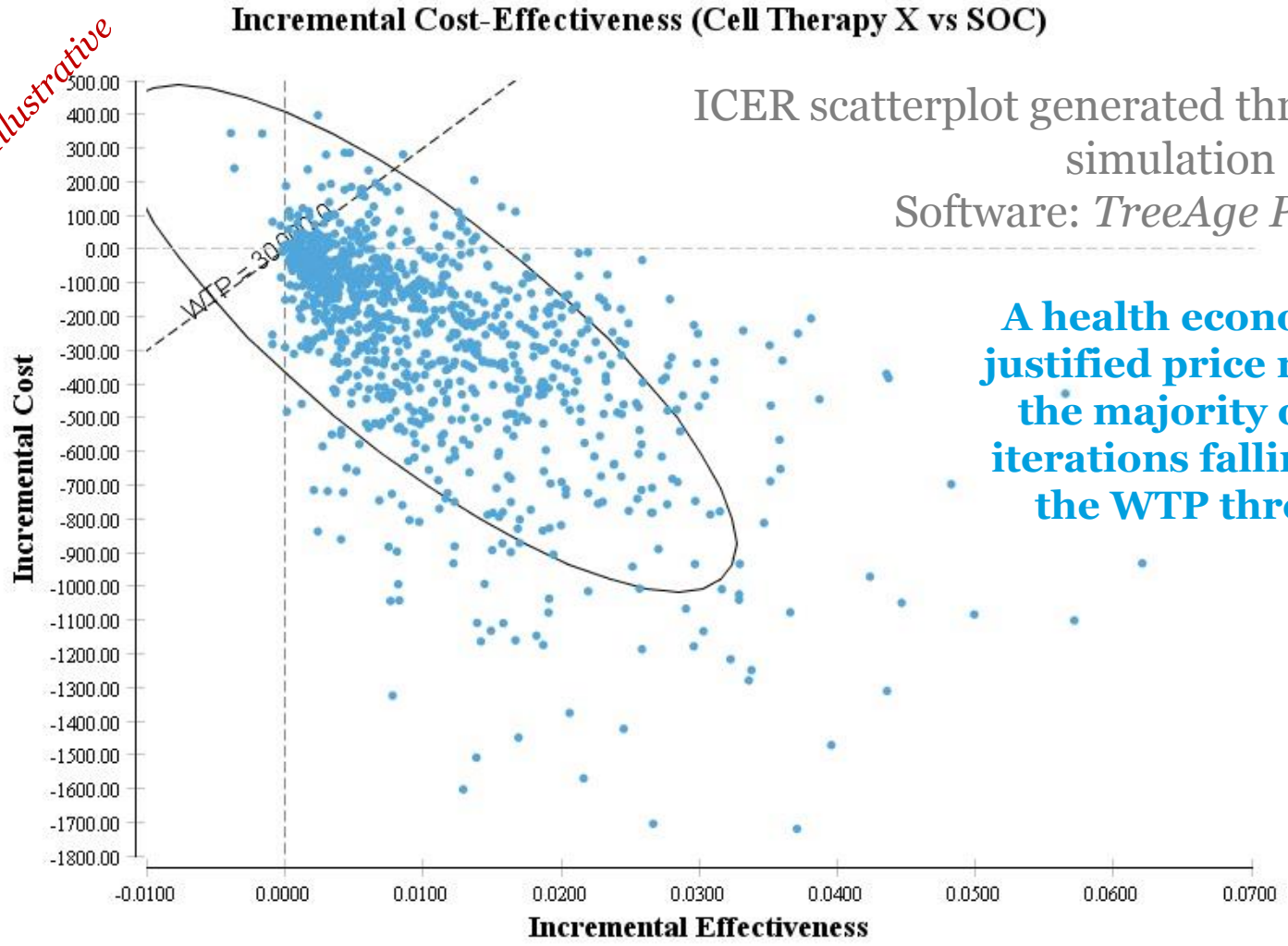
For chronic disease, the CUA horizon can be lifetime; a therapy-specific model is used to capture time-dependent transitions across health states and outcomes

- Health states & transitions: as per disease trajectory
- Time horizon: Up to 100 yearly cycles (discounted)
- Pay-offs: cost, utility, life years
- Sensitivity analysis to address uncertainty
  - Deterministic: univariate / multivariate
  - Probabilistic: parametric / non-parametric (bootstrapping)
  - Structural

- Model type: Decision tree, State transition Markov model, DES, Transmission model
- Analysis: Cohort simulation, Microsimulation

CATAPULT Cell Therapy

Probabilistic sensitivity analysis informs price potential while accounting for uncertainty



ICER scatterplot generated through Monte Carlo simulation

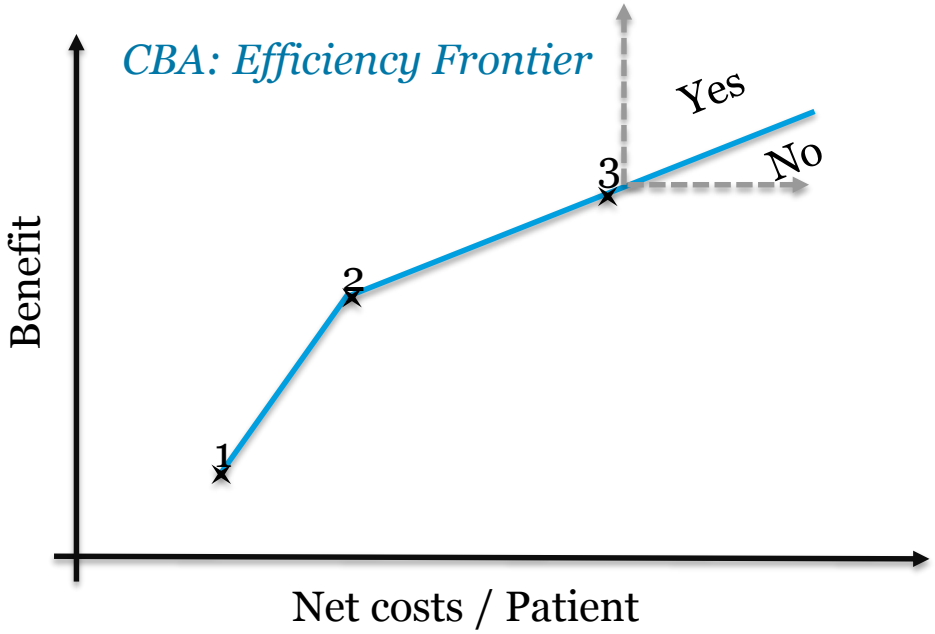
Software: *TreeAge Pro 2014*

A health economically justified price results in the majority of ICER iterations falling below the WTP threshold

CATAPULT Cell Therapy

In Germany instead of cost-utility, a cost-benefit analysis may be applied but only as a last resort

- If added benefit is recognised but agreement on price is not reached:
  - Manufacturers can request cost-benefit analysis to avoid international price-referencing (to EU15 average)

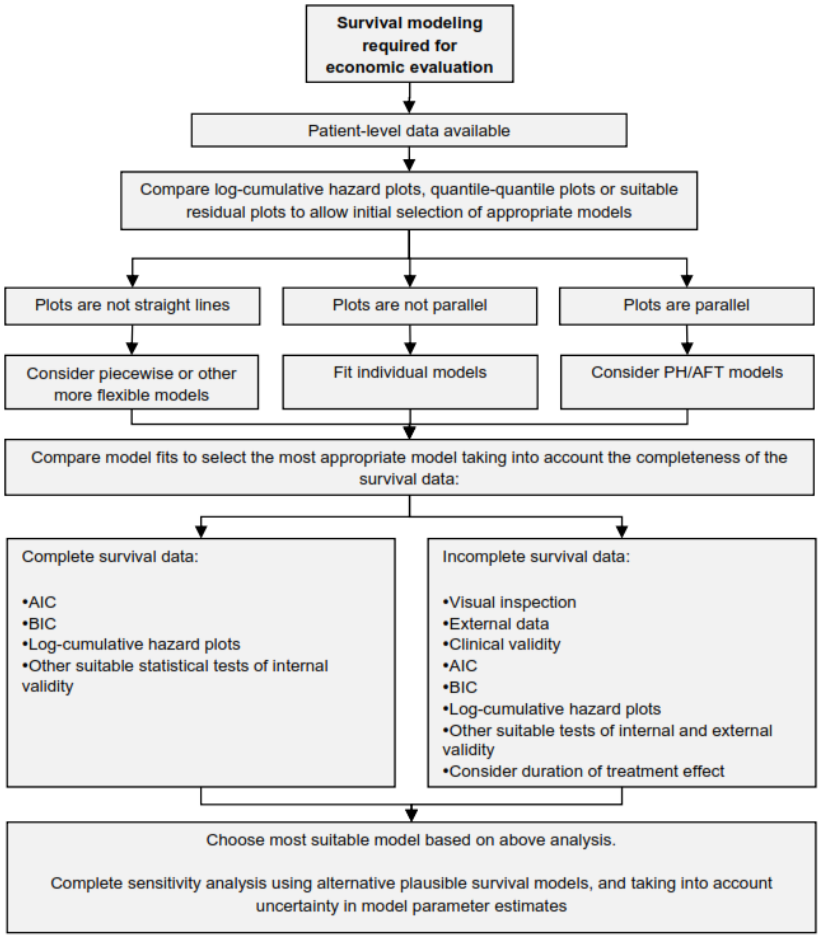


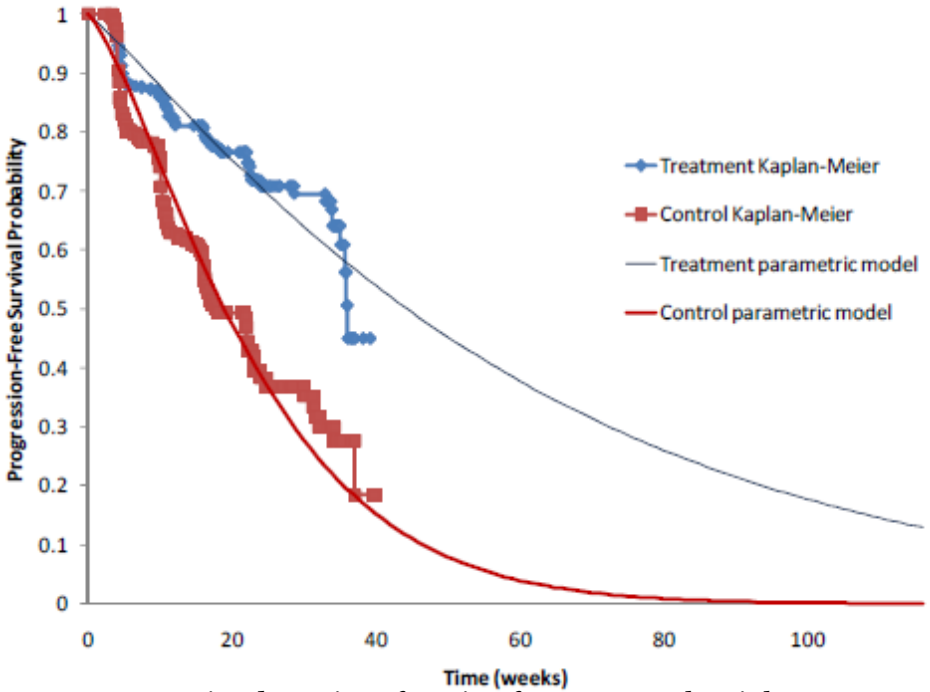
- Costs & benefits of currently commissioned treatments (e.g. 1-3) define the efficiency frontier (blue line) i.e. the willingness to pay (WTP)
- New treatments exceeding the existing cost and benefit levels can be considered acceptable if they are above the extension of the WTP

CATAPULT Cell Therapy

Across Big5EU, only in UK there is clear HTA guidance on how long-term claims can be substantiated through extrapolations

- To bridge the gap between short-term data and long-term claims a regression framework is applied
  - Specified parametric and semi-parametric models are fitted
  - Optimal model selected based on statistical considerations and biological plausibility





Fitted survivor function for an example trial

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

To address uncertainty outcomes-based pricing agreements can be employed

- Types of outcomes-based pricing agreements in operation:
  - Cohort - based
    - Adjust price based on real world evidence
  - On individual patient basis

    e.g. ChondroCelect in Spain:
    - 100% refund if failure at year one
    - 75% refund if failure at year two
    - 50% refund if failure at year three

Conditional on generation of "Real World Evidence "

Due to high RWE and administrative burden confidential discounts/rebates are implemented more often

CATAPULT Cell Therapy

There is variation across the Big5EU on degree of centralisation of P&R decision-making

Increased Decentralisation

Level	France	Germany	UK	Italy	Spain
National	Centralised P&R at national level (HAS, CEPS)	Centralised P&R at national level (G-BA, IQWiG, GKV)	-	Reimbursed ceiling price negotiated (AIFA)	Reimbursed ceiling price negotiated (AEMPS)
Regional	26 regional health agencies (ARS) Distribute funding to hospitals; little P&R impact	~150 sickness funds (KKs); Distribute funding to hospitals	Regional HTA: • NICE • SMC • AWMSG Regional commissioning for specialised services: • England • Scotland • Wales • Northern Ireland	Funding decision by each of the 21 regions *EXCEPTION:* therapies achieving 'innovative' classification by AIFA must be funded Can negotiate price down	Funding decision by each of the 17 regions Can negotiate price down
Local	Hospital funding negotiations / Discounts				

Following reimbursement decision hospital adoption of costly therapies may be delayed due to complexity of securing funding

- Funding mechanisms:
  - Short-term: Provide supplementary funding
  - Long-term: Revise / create new DRG (diagnosis related group) tariff

Country	Supplementary funding for hospital products
France	• Funding *(Hors T2A)* restricted to: • ASMR I-III, *or* ASMR IV-V against a comparator with ASMR I-III
Germany	• Temporary funding (*NUB*) set locally; Permanent funding (ZE) set nationally
Italy	• Tariff set regionally (File F)
Spain	• **Rarely granted by regions: hospitals have to absorb costs** (impacting uptake!)
UK	• Agreed regionally • Cancer Drugs Fund (£340M p.a.) in England for therapies without NICE endorsement

Launch strategy should account for meeting deadlines for supplementary funding applications

CATAPULT Cell Therapy

Other categories:

Minimally Manipulated Cell Therapies
Hospital Exemptions
Compassionate Use

CATAPULT
Cell Therapy

Other regulatory categories and main differences from the P&R processes described for licensed ATMPs

Minimally manipulated cell therapies (MMCs)

- In France, Germany and UK same P&R assessments apply to MMCs and ATMPs
- In Italy and Spain, MMCs can bypass national/regional P&R assessments and be assessed by hospitals only

Hospital exemptions / Specials

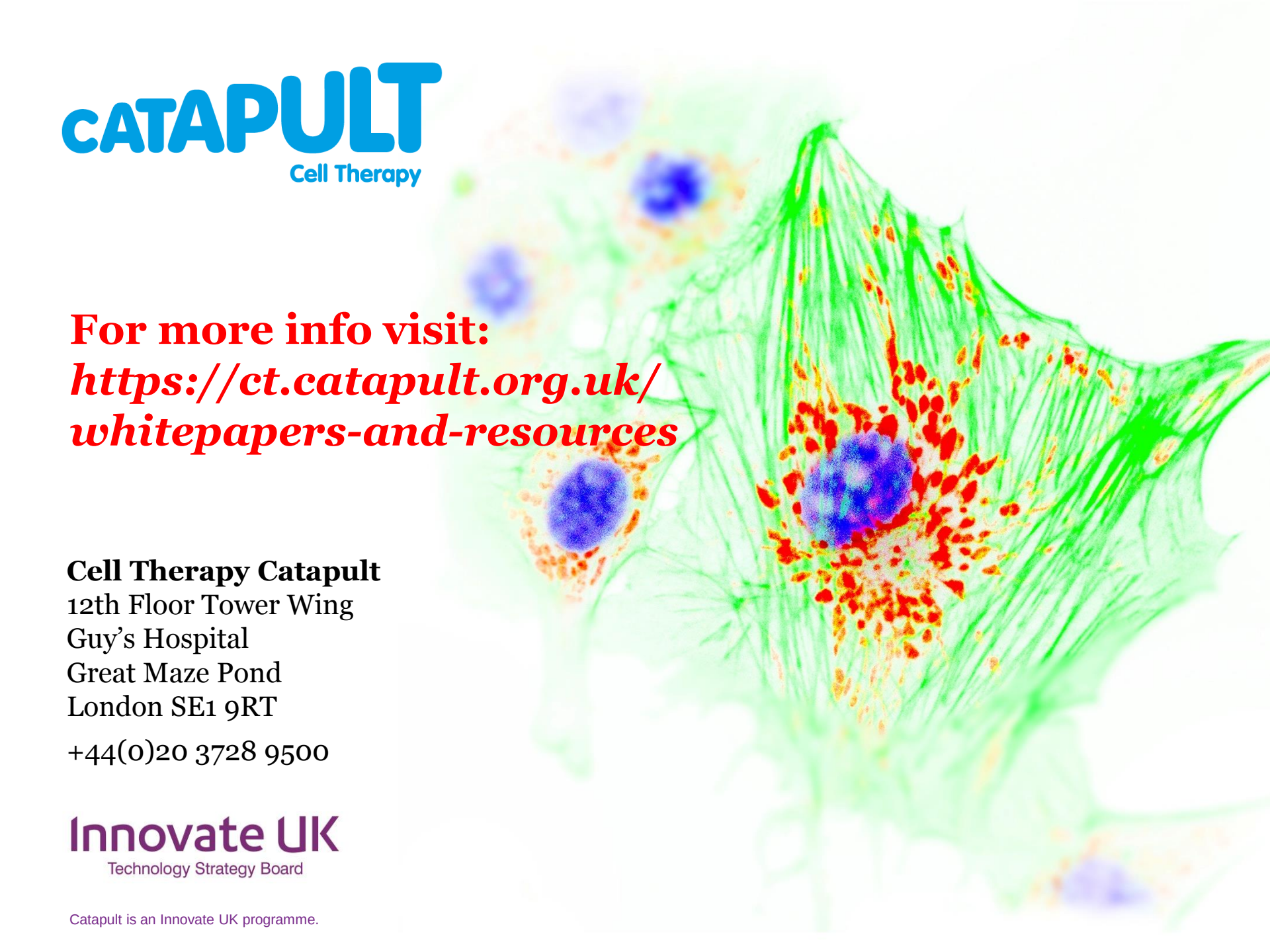
- Price often determined on a cost-plus basis (rather than value-based)
  - Exception Spain: Need to be supplied on a not-for-profit basis

Compassionate use

- In Germany the manufacturer has to provide treatment free of charge
- In the other 4 markets price is set freely
  - In France, free-pricing can be penalised through post-launch rebates (ATU)

CATAPULT Cell Therapy

CATAPULT
Cell Therapy



For more info visit:
https://ct.catapult.org.uk/whitepapers-and-resources

Cell Therapy Catapult
12th Floor Tower Wing
Guy's Hospital
Great Maze Pond
London SE1 9RT

+44(0)20 3728 9500

Innovate UK
Technology Strategy Board

Catapult is an Innovate UK programme.