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Opportunities and challenges with performance based pricing schemes for ATMPs

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Performance based pricing schemes (PBPS) may include one or more of the below arrangements

- Performance linked reimbursement
  - Reimbursement based to one or more of the following outcomes (over a specified period):
    - Clinical outcomes achieved
    - Financial or utilisation outcomes
    - PROs
- Coverage with evidence development
  - Coverage provided further evidence is collected from a pre-specified study
- Conditional treatment continuation
  - Continuation of coverage for individual patients meeting treatment goals

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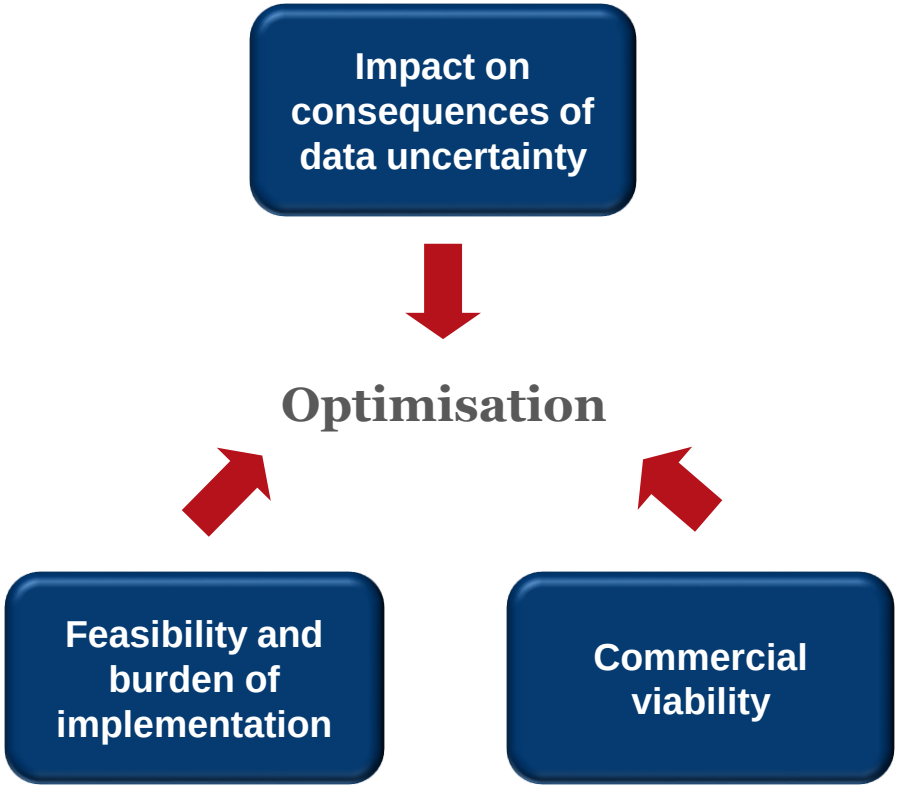
Three key considerations in selecting a PBPS



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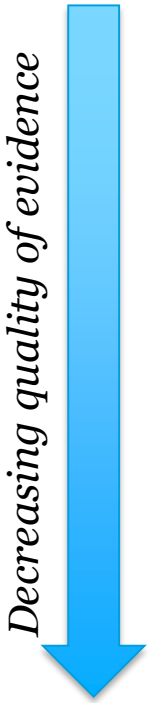
Common challenges with ATMP supporting data at launch impacting reimbursement negotiations (I)

- Demonstration of incremental benefit over SOC/BSC may be limited by clinical feasibility and regulatory constraints e.g.



  - Gold-standard H2H trial design may not be possible
  - Randomised placebo controlled trials may not be feasible
    - Limits prospect for credible indirect comparisons
  - Meaningful comparative data from single arm trials may not be feasible due to limitations with:
    - Historical control data
    - Natural history of disease is not well known
    - Patient population heterogeneous
  - No comparable treatment and measures of outcome are available

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Common challenges with ATMP supporting data at launch impacting reimbursement negotiations (II)

- Short-term data at launch
  - Uncertainty on long-term maintenance of effect
  - 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*)

Many of the challenges faced by ATMPs are not unique to these technologies The uniqueness is that these medicines face a higher concentration of these problems

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Data uncertainty impacted the outcomes of all ATMP assessments by NICE so far

Therapy	Data uncertainty	Decision
ChondroCelect and MACI *(for knee cartilage repair)*	Lack of robust evidence on long-term incremental benefit vs the SOC (microfracture)	Restricted use; For patients with no previous knee repair surgery, ≤minimal OA damage, defect›2cm² Due to prolonged HTA by NICE and similar challenges across Europe, the MA of the former is withdrawn and the latter suspended
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
Holoclar *(for moderate to severe unilateral or bilateral limbal stem cell deficiency due to burns)*	The historical controls used resulted in weak incremental benefit evidence vs conjuctival limbal autograft; scarce clinical data on bilateral burns	Restricted use; to 1 eye and provided that patient already failed conjuctival limbal autograft or not suitable for it; confidential discount mandatory on published price of £80K/eye

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

1. Conditional Reimbursement: The Cancer Drug Fund

2. The "extrapolation process selection algorithm" by NICE DSU * on how survival data could be credibly extrapolated beyond trial duration

3. Using outputs from the cost-utility framework to quantify payer uncertainty; subsequently 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" NICE DSU, January 2016

Today's focus

*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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The three uncertainty metrics recommended by NICE as a basis for identifying MEAs that reduce payer uncertainty

Output	Value
Probability of being CE	• Measures through probabilistic sensitivity analysis the % of ICER scenarios falling below the WTP threshold
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

At population level

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MEAS involving payment adjustments of various kinds (from discounts to outcomes-based) can optimise uncertainty metrics

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*

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

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OHE recently* questioned the appropriateness of measuring consequences of decision uncertainty

- The consequences of decision uncertainty is calculated using the EVPI framework and therefore it is an expected upper limit of the benefits of more research
- It neither indicates what further research can be feasibly conducted nor the value that this research will bring
- Furthermore if there are few patients and high unmet need it may take years to collect more evidence
  - The impact on patients of such delayed access is not captured by this framework

* *Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose, OHE, February 2017*

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II. Balancing opportunities and challenges with PBPS: *Securing Commercial Viability*

Choosing between MEAs with similar effect on uncertainty

	Manufacturer		
	Pros	**Cons**	
Discount	Faster revenue generation	Large Budget Impact (BI) limits access*	
Rebates			High implementation costs
Annuities	Small BI enables wider access	Slow revenue generation; is it commercially viable? *third party finance?*	

Performance-linked reimbursement

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

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Under the Velcade PBPS, JC rebates the cost of non responders* after 4 Tx cycles; payers have 60 days to submit claims

Key issues at launch:

- Inefficient communication between treating physicians, pharmacists and NHS budget holders
- Delayed submission of claims for non-responders
  - The 60-day claim period was too tight resulting in missing claims
- In ~50% of cases refunds received had not been passed onto the originating budgets (PCTs at the time)
- Velcade was not ceased in some non-responders; further expenses accrued

Key learnings:

- Needed to fund staff time to administer scheme and prevent missed claims
  - Average time taken to administer the scheme per patient treated: 37.5 minutes**
- NHS systems needed upgrading to deal with rebates

* PAS agreed in 2007 with Jannsen-Cilag and NHS England/Wales/Northern Ireland for Velcade monotherapy in patients who are at first relapse and who have undergone, or are unsuitable for bone-marrow transplantation; Response measured using serum M protein after 4 Tx cycles; Tx continued only in complete or partial responders i.e. with reduction in serum M protein of ≥50%

** Williamson et al., 2010

The MS risk sharing scheme (UK) exemplifies the challenges of coverage with evidence development

- In 2002 NHS agreed to provide 4 MS drugs with evidence development to inform future policy
- It's a 10-year observational study with a historic cohort as a control; due to delays the final outcome is still pending:
  - It took 3 years instead of the expected 18 months to recruit 5000 patients at 73 centres
  - The 2-year results were not reported until 2009 and were inconclusive
  - The 6-year results were reported in 2015 concluding that treatments were slowing disease progression by 24-40% compared to natural course of history
  - The 10-year results were expected in 2016 but have been delayed
  - The NICE MTA is on hold and subject to proposals by manufacturers on PAS
- The cost of monitoring the scheme has been estimated at £1m a year*

Raftery 2010 BMJ 340:c1672;

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III. Balancing opportunities and challenges with PBPS: *Enabling Implementation (i)*

1st Area of focus: *Following up patients and their progress*

- Feasible approaches to short and long-term patient follow-up; various challenges e.g.:
  - Larger populations and longer periods of follow-up
  - Patient mobility impacting follow-up
  - Patient willingness to be followed up long-term
- Identification of outcomes that are:
  - Meaningful for payers
    - Challenges with differentiating for poor performance due to product vs healthcare provider vs other causes
  - Measurable within an appropriate timeframe
    - Based on horizon of data uncertainty vs claims, and disease area e.g. claim cure from haematological vs solid tumours

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III. Balancing opportunities and challenges with PBPS: *Enabling Implementation (ii)*

2nd Area of focus: *Data collection and management infrastructure*

- Communication processes for timely info flow between physicians, pharmacists, finance, NHS budget holders, manufacturer
- Availability of IT infrastructure/databases for:
  - Capturing IPD while securing patient confidentiality
  - Supporting payment of the correct recipient

    e.g. a rebate reaches originating NHS budget rather than treating hospital
- Timely data analysis to inform payment flow and reassessments
- Auditable infrastructure: the NHS has to audit PBPS

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III. Balancing opportunities and challenges with PBPS: *Enabling Implementation (iii)*

3rd Area of focus: *Resourcing*

- Measure NHS resource requirements to report in proposal to PASLU
- Ensure availability of NHS resources to administer the MEA
  - Need to fund staff to run scheme(s) effectively
- Ensure resources are adequately trained

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Regulatory infrastructure that could be leveraged to facilitate PBPS implementation

- Infrastructure required by regulatory authorities
  - e.g. FDA request for 1000 patient registry collecting data on Kymriah safety (secondary malignancies/AEs) but also on relapses over 15 years
  - Since 2014 EMA has an ongoing registry initiative to
    - Make better use of existing registries
    - Facilitate the establishment of high-quality new registries

Leveraging EMA requirements for registries provides an opportunity for a common CED platform across EU markets

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NHS infrastructure that could be leveraged to facilitate PBPS implementation (UK)

- Data collection infrastructure mandated by NHS England e.g.
  - Databases of the National Cancer Registration and Analysis Service e.g.
    - SACT database (systemic anti-cancer treatment data);
      - Patient and tumour characteristics
      - Treatment characteristics and outcomes
      - Trust and consultant details
    - Other databases: DID (diagnostic imaging dataset); CWT (cancer waiting times)
  - Infrastructure for CDF
  - Existing registries e.g. the British Society of Blood and Marrow Transplantation registry
    - Outcomes including blood cancer remission at 100 days post-transplant, annually for first 10 yrs, every 2 yrs for yrs 11-20, and every 5 yrs thereafter
- The upcoming Advanced Therapy Treatment Centres
  - Aimed at establishing best practice for patient follow-up and data capture

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Existing infrastructure that could be leveraged to facilitate PBPS implementation (other markets)

- Italy: Existing AIFA infrastructure allows registry inclusion at €30,000* p.a. per product/target indication
  - More than 120 registries were reported*
  - Web-based AIFA Registry is a tool customized for individual drugs, allowing:
    - Registering patient eligibility and outcomes
    - Hospital pharmacists to dispense the drug and charge relevant budgets
    - AIFA to evaluate drug effectiveness in real world
    - Companies to manage innovative pricing agreements
- US: CMS national coverage determinations under the coverage with evidence development arrangement

Risk-sharing schemes more common in single payer markets (Europe, Canada, Australia) but now also in US under CMS

** OHE, Multi-indication pricing, Ferrandiz et al., October 2015*
*** ISPOR, PRS66, November 2015*

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