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How uncertainty around the value claims of cell and gene-based immunotherapies can be addressed in payer negotiations

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Common sources of ATMP data uncertainty at launch impacting payer 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
- 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

…<u>BUT</u> high reimbursed prices need to be secured for commercial viability

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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 and address uncertainty
    i. “Probability of being cost-effective” and “incremental net health effect”
    ii. The potential introduction of the ”Consequence of Uncertainty” as per:
        - “Exploring the assessment and appraisal of regenerative medicines and cell therapy products”, NICE, March 2016
        - “Framework for analysing risk in HTA and its application to Managed Entry Agreements”, DSU, January 2016
3. Using the above uncertainty metrics in selecting the optimal managed entry agreement (MEA)
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:

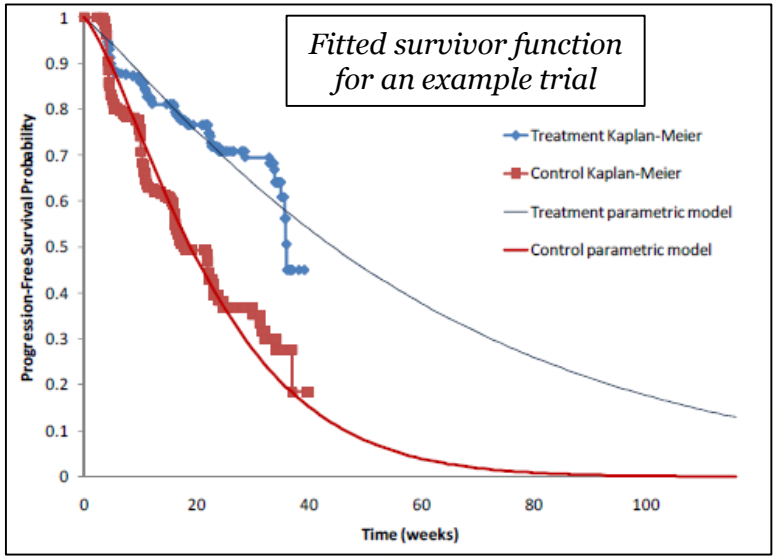
- According to the NICE TA framework, it is mean rather than median survival that needs to inform the lifetime horizon of the cost-utility analysis
  - However such data tend not to be available at launch
    - Therefore estimates of entire survival distributions are required

THE OBJECTIVE:

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

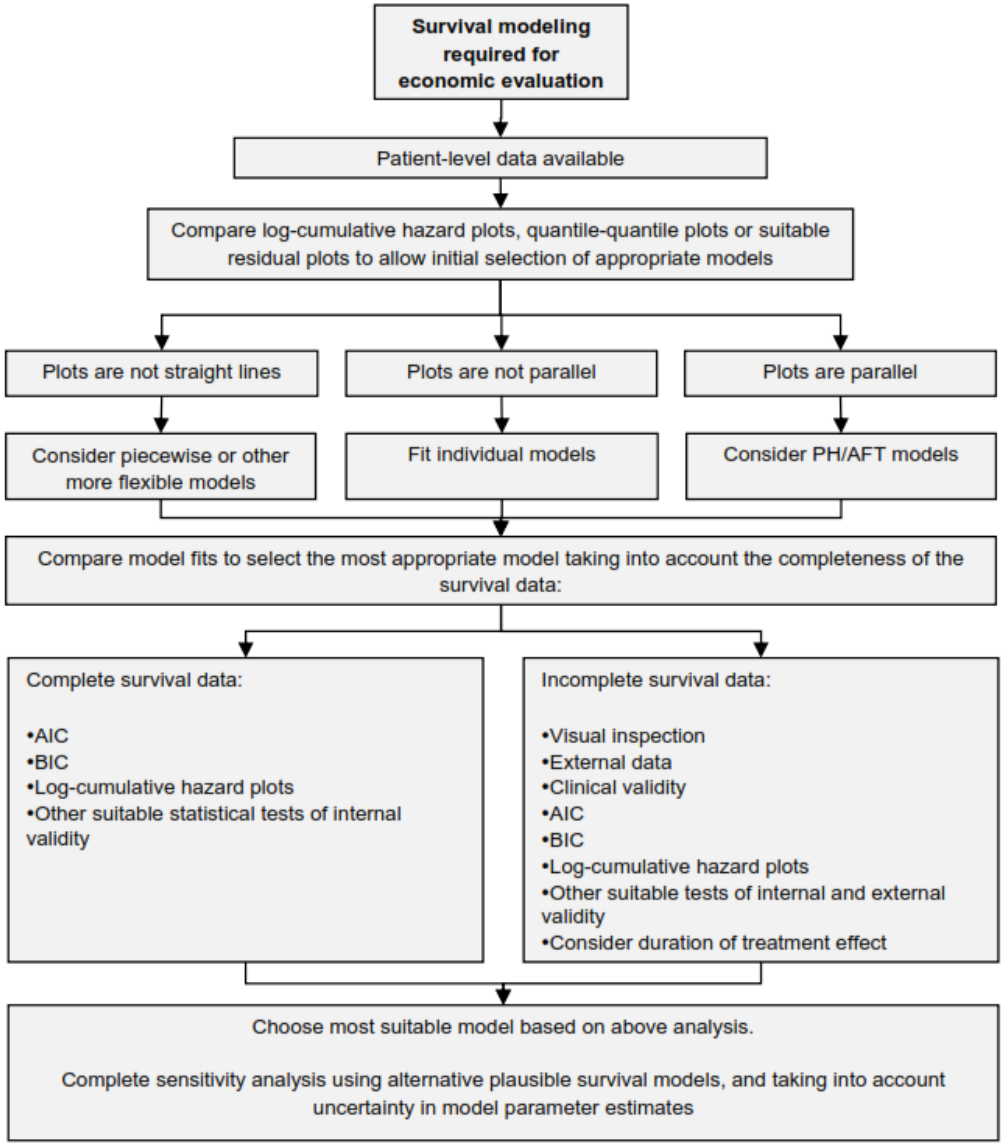
THE PROCESS:

- 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*

Optimal extrapolation framework selected based on statistical considerations and external validity



Individual patient data

Exploratory data analysis

- To inform type of model e.g.
  - Parametric
  - Non-parametric
  - Piecewise

Fit models

(typically: Exponential, Weibull, Gompertz, log-logistic, log normal, generalised Gamma)

Compare models

- Statistical measures of model fit to observed trial data
- External data
- Biological Plausibility
- Clinical expert opinion

Choose optimal model

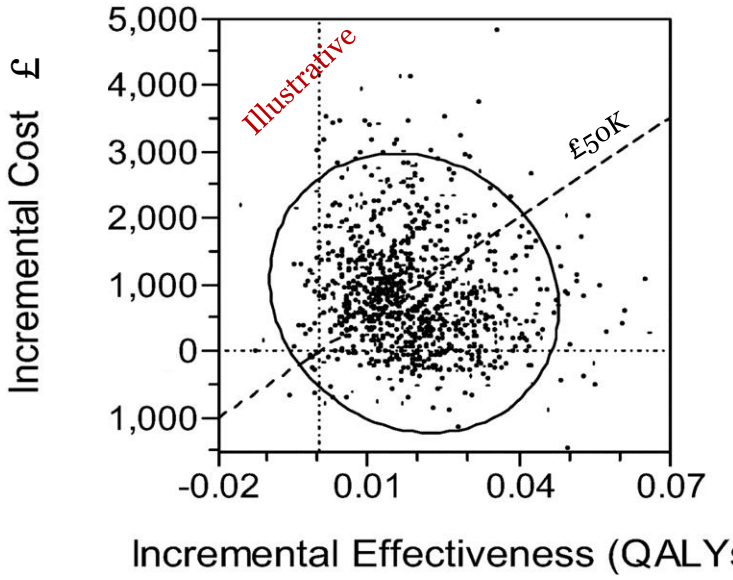
Sensitivity analysis

- Using alternative plausible model scenarios

PH; proportional hazards; AFT; Accelerated Failure Time

Using the cost-utility framework, magnitude of data uncertainty is quantifiable on the basis of the following two metrics

A. Probability of not exceeding the ICER threshold (based on probabilistic sensitivity analysis)
   - No defined threshold: ≥70% probability of being CE is considered of low uncertainty



% of iterations ≤ICER threshold

B. Incremental Net Health Effect (NHE) expressed in monetary or QALY terms; it is the mean value across all iterations

Incremental NHE = [(Incremental Effectiveness) x (ICER threshold)] –[Incremental Costs]

Accounting for the cost-effectiveness of each iteration

   - NHE should be positive for adoption; the greater, the more likely
   - Incremental NHE is then calculated at population level and over the technology time-horizon

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A new uncertainty metric has been proposed*: *"Consequences of decision uncertainty"*

Comparing Treatment A vs B

Illustrative

Scenarios (PSA iterations)	Treatment Net Health Effect (NHE) in terms of QALYs		Optimal Choice (based on QALY maximisation)	Opportunity Loss when choosing B vs A (in QALYs)
	A	***B***		
1	9	12	B	0
2	12	10	A	2
3	14	20	B	0
4	11	10	A	1
5	14	13	A	1
Mean value across all scenarios	**12**	**13**	**B**	**0.8**

Consequences of decision uncertainty
at individual patient level
(can then be used to calculate at population & technology time-horizon level)

* "Exploring the assessment and appraisal of regenerative medicines and cell therapy products", NICE, March 2016; "Framework for analysing risk in HTA and its application to Managed Entry Agreements", DSU, January 2016

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What drives a large consequence of uncertainty

	Cell & Gene-based immunotherapies
• Uncertainty in clinical and economic outcomes ○ Exacerbated when long-term claims are made on the basis of short term data	✚ ✚ ✚
• High acquisition cost	✚ ✚ ✚
• Large target patient population	✚

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What can contribute to a positive recommendation by NICE TA committees

Parameter	Value
NHE	• Should be a positive value ○ The larger, the more likely the adoption
Probability of being CE	• No defined threshold • ~70% probability of being CE is considered of low uncertainty (based on past TAs)
Consequence of uncertainty	• No defined threshold • Should be much smaller than the NHE ○ The smaller the more likely the adoption

Proposed new metric

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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
- 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	Price discount likely Large Budget Impact (BI) limits access*	Price reduction	Is there a reliable process to inform rebates? Can the manufacturer pay rebate?
Annuities	Small BI enables wider access	Slow revenue generation; is it commercially viable?	Reduced annual BI	Admin. burden

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

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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