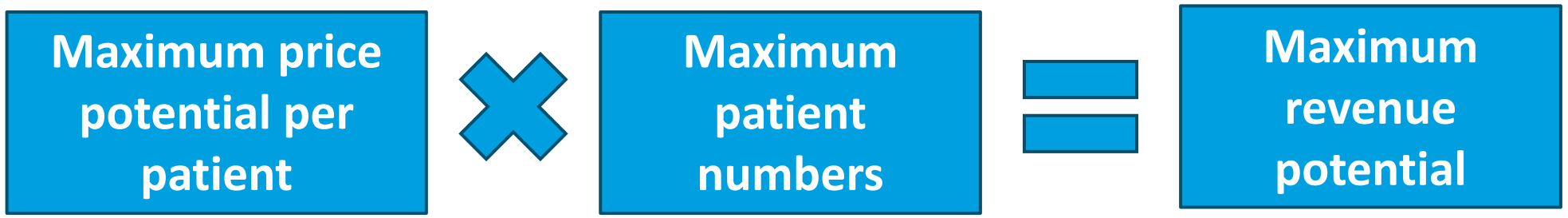
Informing strategic decision-making in early clinical development: Exploring commercial potential

The choice of target patient population is one of the most important strategic decisions informing early clinical development

- The choice of indication and therapeutic position to target or prioritise has substantial impact on the commercial opportunity a novel therapy presents
- The commercial opportunity is impacted by:
  A. **The Headroom for innovation**, i.e. the maximum price potential of cure per patient in a given indication/ therapeutic position
  B. **The size of the target patient population**, i.e. the maximum volume opportunity
- A and B are subsequently used to inform maximum revenue potential and determine how commercial opportunity varies across different patient populations
  - This allows us to compare the relative commercial opportunity of different target patient populations, to help inform the strategic decision-making around which population to pursue (first) in clinical development and define the inclusion criteria for the first-in-human clinical trial



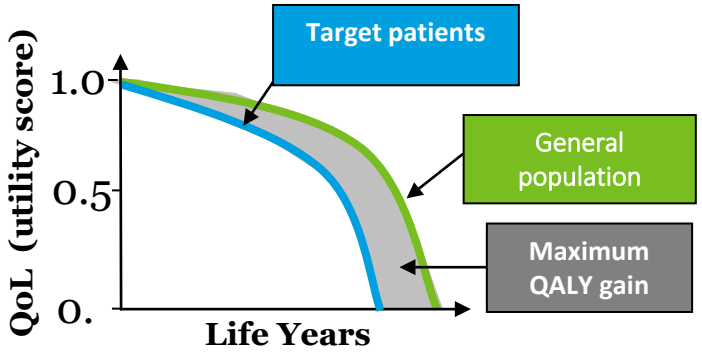
The cost-utility analysis (CUA) framework is central to our methodological approach

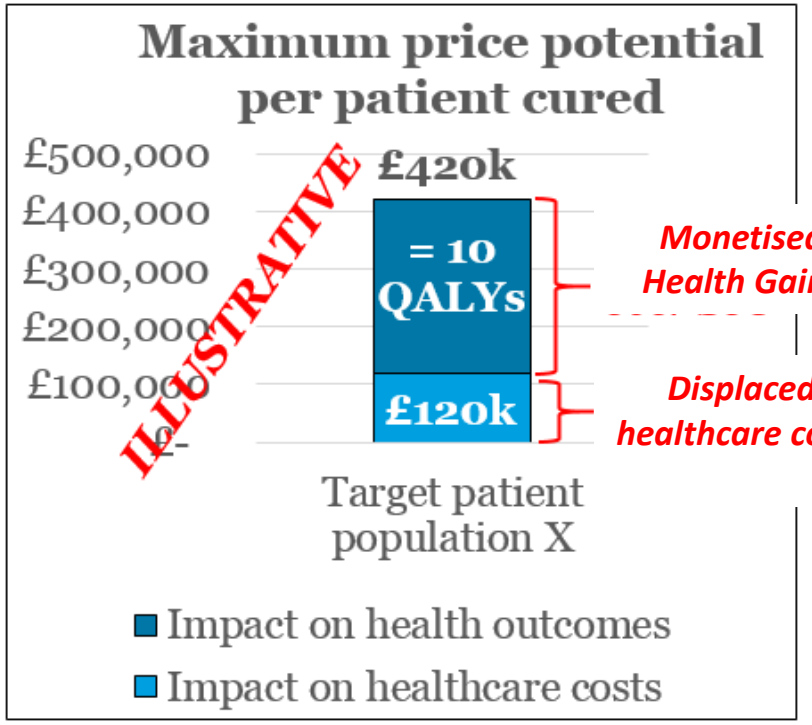
- The value proposition of ATMPs involves long-term claims of clinical and economic benefits best captured through cost-effectiveness analysis
- The CUA framework is used to inform reimbursement decisions in several countries; we typically use the UK as the reference market for our analysis:
  - the WTP/QALY is explicitly defined
  - UK HTA assessments have international impact
  - directional early pricing insights are sought
- We extend the UK analysis to USA, Canada, Australia where CUA plays a role in reimbursement decisions by accounting for country-specific differences in:
  - Healthcare costs (using OECD Purchasing Power Parities [PPP] for health)
  - WTP/QALY (for the US, in line with the Institute for Clinical and Economic Review [ICER] framework; for Australia and Canada based on past HTA decisions)
- ATMPs launching so far (unlike traditional medicines) follow a tight price corridor across major European markets; therefore prices in markets where CUA is not followed closely resemble prices determined in CUA markets (making CUA a relevant framework for early-stage cross-border ATMP pricing insights)
  - We obtain directional pricing insights across the remaining of the Big5EU by adjusting UK price potential using OECD PPPs for health
  - These could be used for validation in payer research

We use the cost-utility analysis (CUA) framework to estimate the Headroom for innovation (Hfl) – i.e. the value of cure per patient

Value of cure/ Headroom for innovation (Hfl) = Healthcare costs displaced + monetised health gains

- The Hfl analysis estimates the value of cure in terms of:
  - A. **Impact on healthcare costs:** Eliminating the need for current therapeutic approaches
  - B. **Impact on health gains:** The maximum gain in Quality-Adjusted Life-years (QALYs)
    - The QALY gain accounts for improvements in quality of life (QoL) and life expectancy to match that of the general population
    - We monetise the QALY gain by applying country-specific levels of willingness to pay (WTP) per additional QALY
      - The WTP is explicitly stated in certain countries, e.g. in England (most commonly £20-30k/QALY and up to £300k for extremely rare conditions)
      - In countries where the WTP/QALY is not explicitly stated, review of recent HTA and pricing decisions provide direction

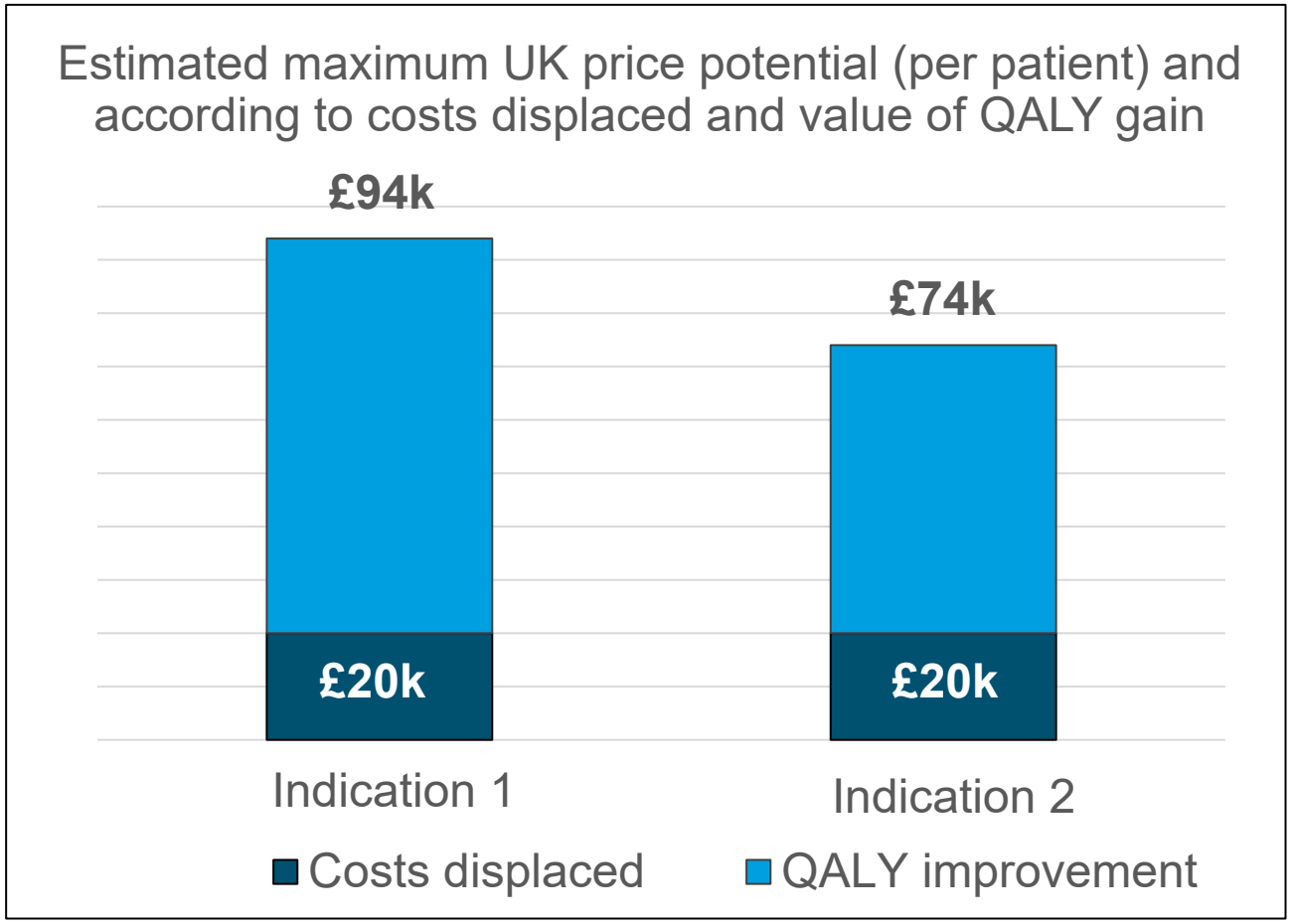




Case study: Informing indication selection through the Headroom for Innovation (HfI) analysis

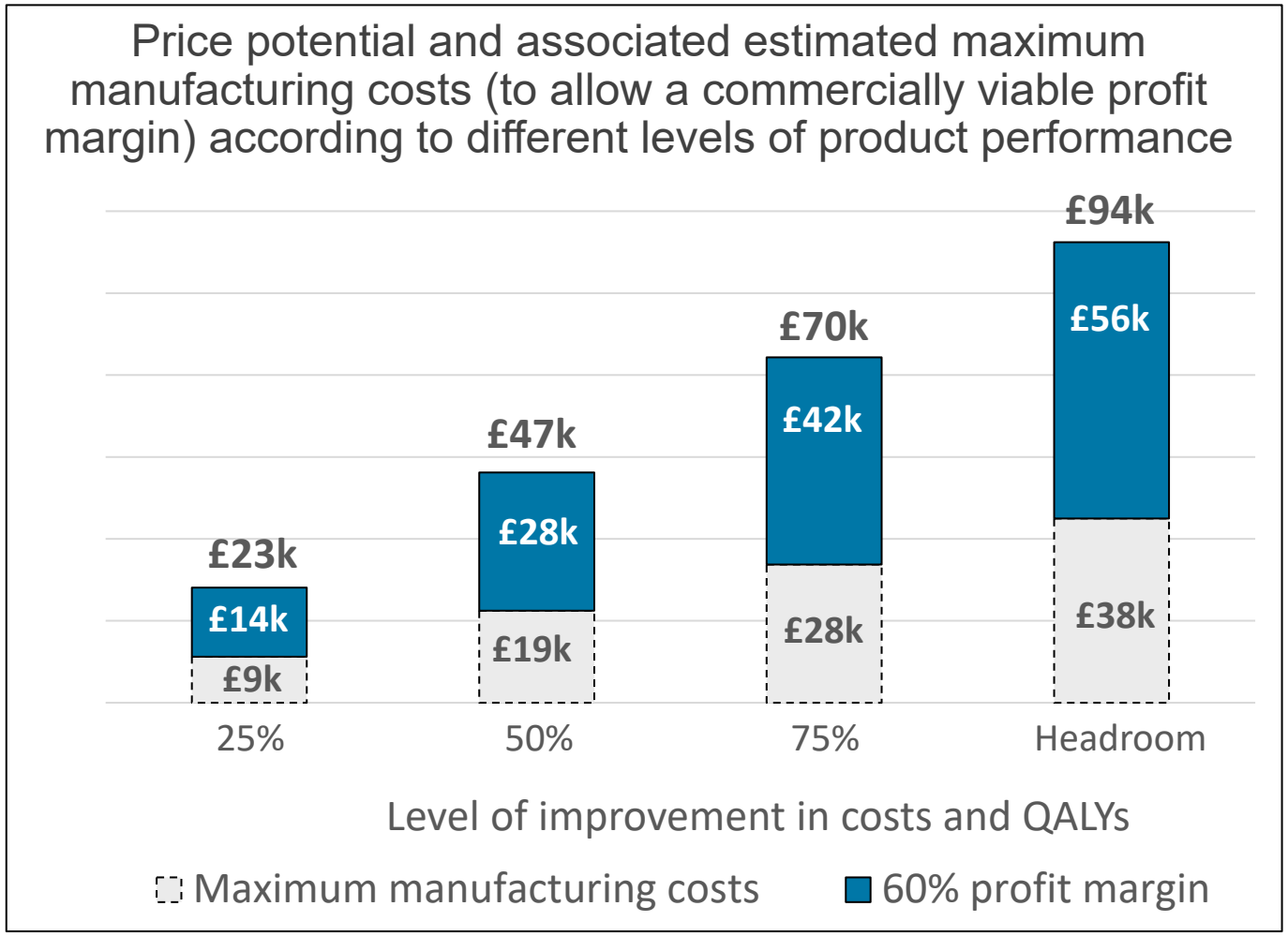
Case study: identifying the maximum price potential (Headroom for innovation) in different target patient populations

- A targeted evidence review informed the CUA, detailing the lifetime cost and QALY implications for patients treated with the current standard of care (SoC) in Indication 1 and 2
- The CUA showed the current SoC for both indications to be moderately priced at £20k for the patient's lifetime, and associated with highly detrimental patient outcomes, meaning there is considerable scope for improvements in QALYs
- The main driver of the price potential in both indications is improvements in health (measured as QALYs)
- The price potential per patient is higher for Indication 1 than 2, but potential patient numbers would also have an impact on commercial opportunity

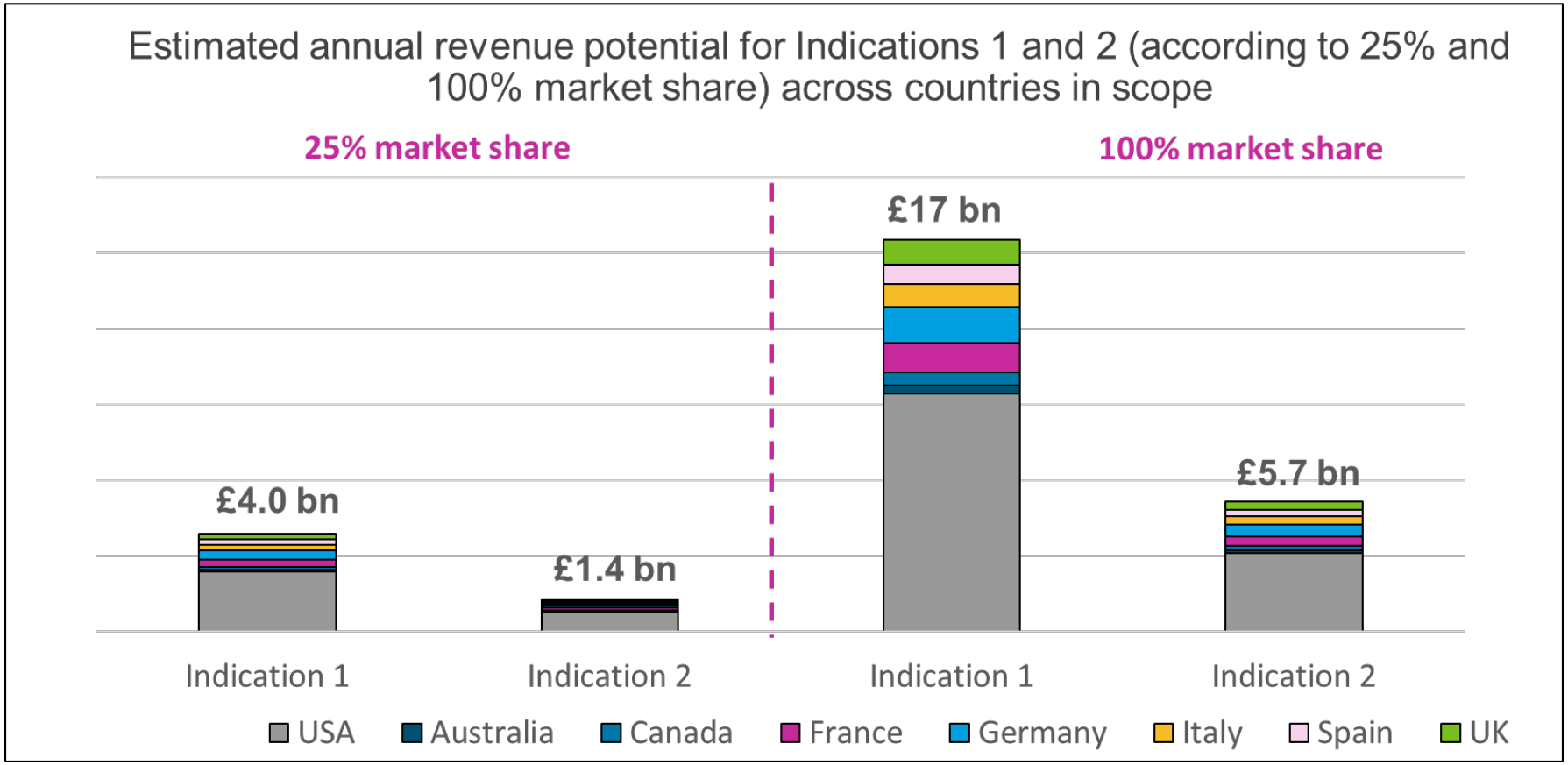


The manufacturing cost threshold analysis explores whether a commercially viable profit margin is achievable and how it is impacted by product performance

- The considerable unmet clinical need in the target indications translate to a considerable price potential even in the absence of cure
- The analysis shows that a 60% profit margin can be accommodated, and still allow for manufacturing costs <£20k, if 50% of the value of cure can be demonstrated
- There is a risk that if the QALY gain does not exceed 25% of the maximum value of cure, the product may not be commercially viable
- This information can help determine the decision-making criteria for progressing through the stages of therapy development once early indicators of clinical performance are gained



The resulting revenue estimates show that Indication 1 has the greater commercial potential (driven by higher patient numbers)



- Patient numbers for each indication were derived from a review of epidemiological studies and extrapolated to the countries of interest when country-specific numbers were not available
- Revenue potential was estimated from patient numbers, headroom price, and estimated market share

The impact

- The analysis provided the manufacturer with insights on the relative commercial attractiveness of the two indications
  - This helps inform the decision of which indication to prioritise in clinical development
- The Headroom for innovation analysis identified the relative strength of the key value drivers in the target indications (i.e. QALY benefits vs. cost impact)
  - This helps inform the key outcomes that need to be collected during clinical development to optimise the value proposition of the novel therapy
- Although the manufacturer was uncertain at the time of the analysis about the exact magnitude of manufacturing costs, our analysis informed the thresholds not to be exceeded and how these vary across different product performance scenarios
  - This allowed the manufacturer to define 'go'/'no-go' decision-making criteria for clinical and manufacturing strategy development i.e.
    - Endpoints that need to be met in clinical development and the corresponding manufacturing cost thresholds
- These commercial insights fed into the manufacturer's development of the target product profile (TPP) for the novel therapy, alongside clinical, regulatory and manufacturing considerations

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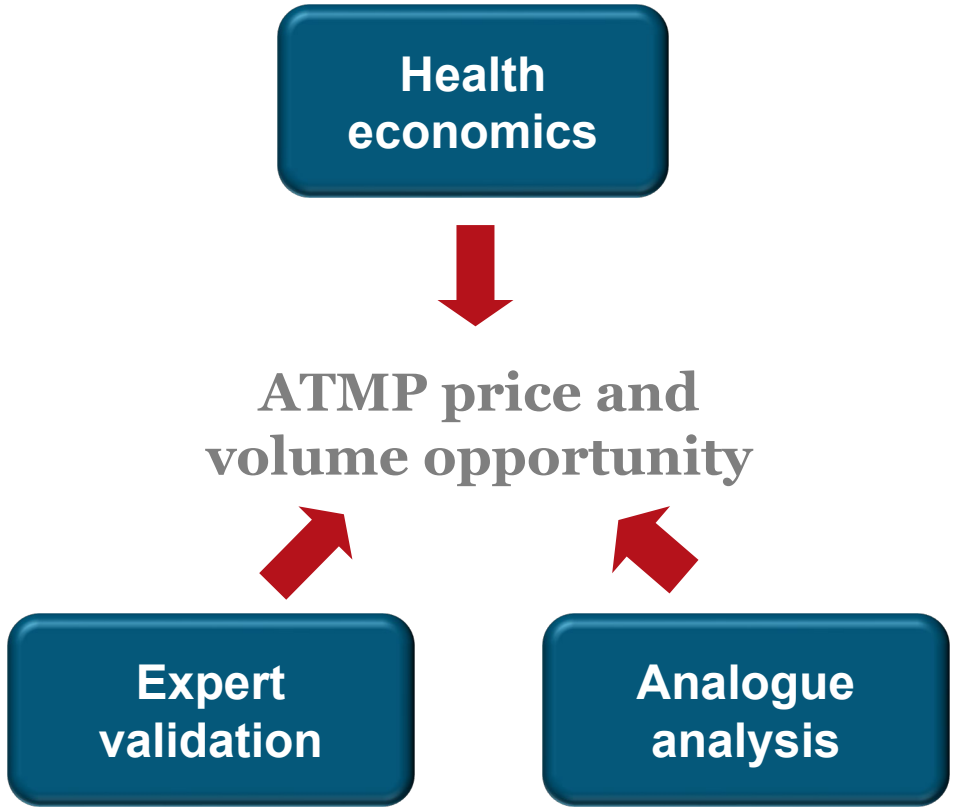
UKRI Innovate UK

Informing evidence generation activities and commercial viability through detailed health economic analysis

We leverage multiple methodological frameworks to support the optimisation of ATMP value proposition

- Health economics:
  - Cost-effectiveness and budget impact analyses
  - Sensitivity analyses
  - Data uncertainty management
- Analogue analyses:
  - Secondary research of relevant HTA and commissioning decisions to elicit willingness to pay and adopt
  - Expert validation:
    - Interviews with payer and clinician experts to determine willingness to pay and affordability
- Via qualitative/ quantitative pricing methodologies
  - How to maximise adoption potential through optimisation of value proposition, evidence generation plan, and innovative pricing and reimbursement schemes
  - Detail the need for healthcare system process re-engineering and clinical infrastructure to facilitate adoption



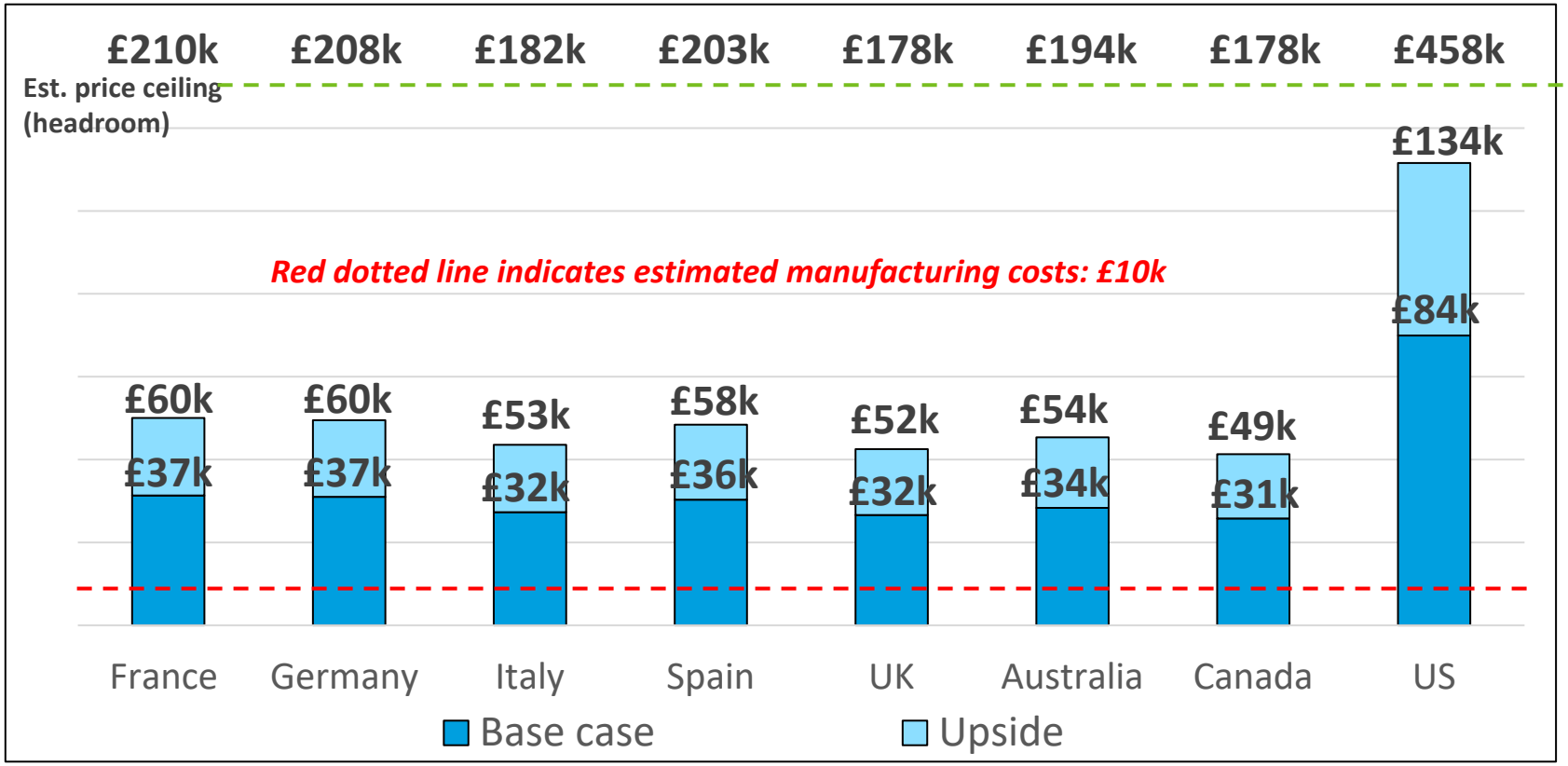
Case study: identify commercially viable parameters of product performance and support evidence generation activities

- A target product profile (TPP) outlined the aspirational performance of a new technology by estimating its expected impact on a range of surrogate, composite, and hard outcomes compared with the current standard of care
- A detailed health economic analysis was developed following a pragmatic review of the literature including previous clinical trials and cost effectiveness analyses
  - In particular, a surrogate outcome and a disease-specific functional measure needed to be explored as potential drivers of hard outcomes in the model. The CGT HEMA team provided potential solutions based on the findings of the targeted evidence review, and through discussions with the manufacturer decided on a specific set of outcomes to include in the health economic models for the target indication.
- A Markov state transition model was built to run through a lifetime horizon, to capture the long-term cost and health impacts compared to the current standard of care (SoC) from the healthcare system perspective

Target Product Profile		**Scenarios analysed**		
	Key outcomes	Base case	Upside	Headroom for innovation
Driven by improvements in surrogate outcome	• Disease-related hospitalisation • Disease-related major event • Death (disease-related and non-disease-related)	20% relative risk reduction (RRR) vs. SoC on each outcome	50% RRR vs. SoC on each outcome	AS PER DISEASE-FREE PATIENTS
Driven by improvement in disease-specific functional score	QoL	20% of patients improve one disease-specific functional score	50% of patients improve one disease-specific functional score	All patients achieve and retain optimal disease-specific functional score
	Cost of routine disease management			

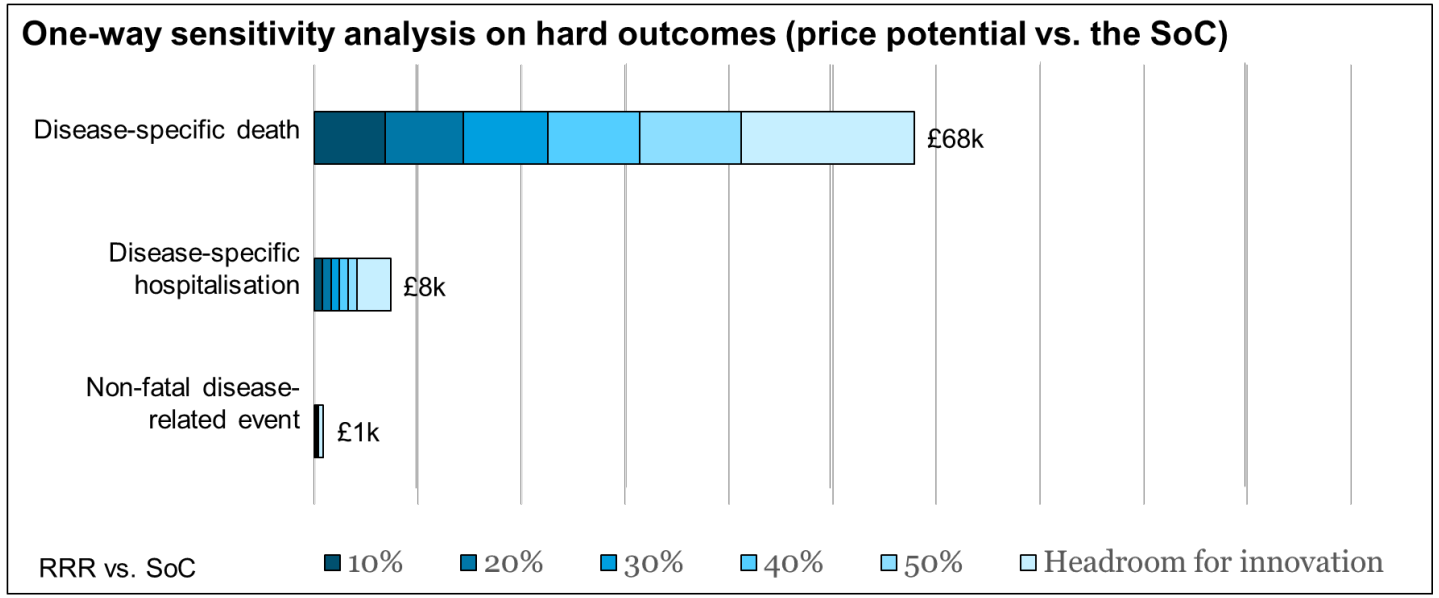
The price potential in EU-5, Australia, Canada and US was calculated from the lifetime net costs and QALYs, and each country's WTP

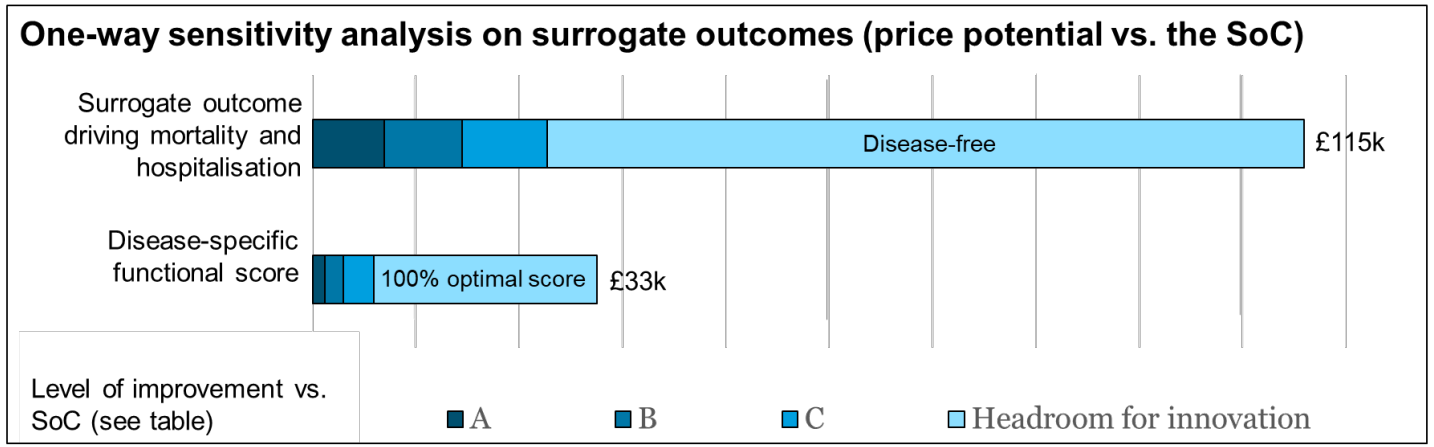
- Price potential across Europe was in the range of around mid £30k for the base case and up to £60k for the upside scenario; higher price potentials for the US are consistent with a higher willingness to pay for healthcare
- Compared to the manufacturing costs, the prices identified were considered commercially viable, achieving a margin of over 60%*



*This figure is a proxy and it is based on historical discussions with manufacturers of ATMPs that Catapult have engaged with over the past 8 years of operations – it is only indicative and based on minimum profit margin aspirations for commercial viability. Although we use the term "manufacturing cost" for simplicity, this cost also includes supply chain and all other operational costs associated with producing and making therapy available to hospitals; for ATMPs the vast majority of these operational costs are typically manufacturing costs. It should be noted that since the purpose of our analysis is not to assess Return-On-Investment, we do not account for R&D costs.

The key value drivers of the price potential were identified through one-way sensitivity analysis





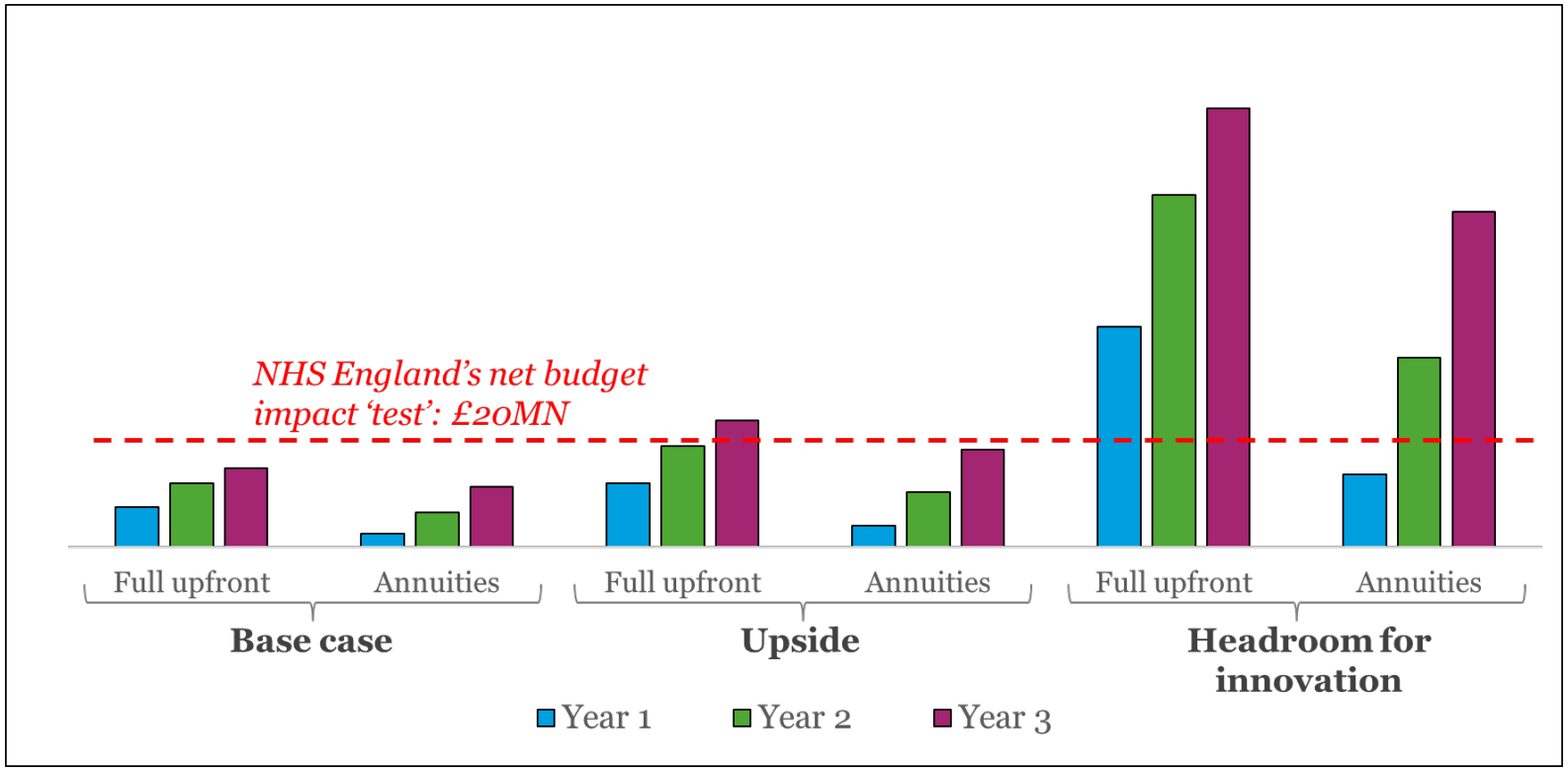
- To understand the greatest drivers of price potential, the relative risk of each outcome was varied in comparison with the standard of care
- As the surrogate outcomes were drivers of hard outcomes, this was done separately for each type of outcome, to avoid double-counting of effect

	Level of improvement vs. SOC			
Outcome	**A**	**B**	**C**	**Ceiling**
Surrogate outcome driving mortality and hospitalisation (baseline X%)*	X+5%	X+10%	X+15%	Disease-free
% of patients improving one functional class**	20%	50%	100%	All achieve optimal functional score

* Each 5% improvement is associated with 9% RRR in mortality and hospitalisation
** Drives QoL (utility) scores and costs of routine disease management

In England, the budget impact of a therapy in the first three years also restricts price potential, the impact of payment schemes was assessed

- The net budget impact of the therapy was calculated from estimated target patient numbers, the displaced costs compared to the current standard of care, and the cost-effective price in three scenarios of product performance
- This therapy was particularly susceptible to budget impact issues as it was for a non-rare condition
- The net budget impact was compared to the NHS threshold of £20m per year for the first three years from launch
- The results show that it may be a challenge to keep net budget impact below the threshold in the third year with prices higher than identified for the base case even if payments are spread over time (e.g. through the use novel payment schemes)
  - In those product performance scenarios commercial negotiations with NHS England may be needed to modulate price and/or number of patients treated annually



The deliverable gave the manufacturer strategic insights in terms of commercial validation and evidence generation requirements

Commercial Validation

- The relationship between parameters of product performance and price potential
  - A user-friendly Excel model was provided so the manufacturer can see how changes to parameters impact price beyond the scenarios modelled
- Whether the technology is likely to be commercially viable at the performance parameters of the base case (accounting for anticipated manufacturing costs and target profit margins)
- In the context of the UK budget impact test and at the base case price, the net budget impact in each of the first 3-years post-launch is not expected to exceed the £20M trigger-point for commercial negotiations, but higher prices would be a challenge at target patient numbers identified

Evidence generation requirements

- The key value driving outcomes that should be prioritised in evidence generation activities
- Hard outcomes key for the purposes of HTA and maximising price potential at launch
- The importance of generating quality comparative data (ideally via a head-to-head randomised clinical trial) in demonstrating product value, as data available from different registries and studies showed some discrepancies in the outcomes for the SoC
- Claims around long-term benefits for a one-off therapy represents uncertainty for HTA bodies when presented with limited-duration trial data at launch; therefore, measures to mitigate the data uncertainty need to be considered, e.g. long-term follow-up, RWE generation, innovative reimbursement schemes, biological plausibility arguments on sustainability of effect and expert opinions

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