Lessons learnt from the UK project to test new models for evaluating and purchasing antimicrobials

Report from external workshops (July and August 2022)

# Project background

The UK’s five-year [national action plan](https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024) for antimicrobial resistance, published in January 2019, commits to testing a new evaluation and payment model for antimicrobials that addresses global market failures and incentivises the development of new antimicrobials. In July 2019, NICE, NHS England and the Department of Health and Social Care (DHSC) (the ‘project team’) started a joint project to test a novel health technology evaluation approach and commercial framework that sought to capture the value of antimicrobial products to both patients and the NHS (measured in quality-adjusted life years, QALYs). This was undertaken through a NICE-led health technology assessment (HTA) and pays the pharmaceutical companies a fixed annual fee informed by that value and delinked from the volume of medicines used. The new payment structure for the two drugs selected for the project, ceftazidime–avibactam (Zavicefta, Pfizer) and cefiderocol (Fetcroja, Shionogi), took effect from July 2022.

NICE, NHS England, DHSC and the devolved governments are now working with stakeholders to review the approach taken in this project and develop routine arrangements for the evaluation and purchase of antimicrobials for the NHS across the UK. The project team held workshops with stakeholders in July and August 2022 to capture the lessons learnt from the project. Workshop attendees were asked to provide feedback on the:

* procurement process
* model contract
* eligibility and selection criteria
* NICE evaluation.

Workshop participants included representatives from the ABPI and pharmaceutical industry; academic institutions; members of the NICE antimicrobial evaluation committee; the clinical and patient experts who advised the NICE committee; and national and international key opinion leaders (KOLs) in antimicrobial resistance. This report summarises the discussions.

# Summary of stakeholder feedback

## Procurement process

The two products included in the pilot, ceftazidime–avibactam and cefiderocol, were selected following an open competitive procurement process. Two contracts were available: one for an antimicrobial new to the market and a second for an existing product with 2 to 3 years on the market. The invitation to tender was launched in July 2020 and a product for each contract was selected in December 2020. The procurement used a competitive dialogue process. This allowed companies and NHS England to discuss the details of the requirements and the final of form of the contract including the invoice price, usage and key performance indicators. This meant NHS England could refine the specification of the invitation to tender, and the companies could submit their bids from a fully informed position.

Participants recognised that the use of an open competitive tender approach was necessary in the pilot to comply with public contract regulations (PCR 2015), because we were limited to selecting only two products – one new-to-market antimicrobial and one existing antimicrobial. But industry found the process time-consuming and long, and this had knock-on effects for launching other products in their portfolios. Companies would prefer a simpler procurement process, and several stakeholders support the suggestion to award contracts to all products meeting the eligibility criteria rather than looking for a mechanism that narrows down applicants to a single successful supplier.

Companies were grateful for the opportunity to engage in dialogue with NICE, NHS England and DHSC as part of the tender, because of the complexities of evaluating antimicrobials and the novelty of the payment model.

## The model contract

The [contracts](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/models-for-the-evaluation-and-purchase-of-antimicrobials/Contract.docx) apply to England only, and have been agreed for a 3-year period with an option to extend up to 10 years. Purchasing authorities will acquire the antimicrobials using an agreed confidential invoice price, and NHS England will subtract the costs of these purchases from its quarterly payments to the company. The contracts also stipulate conditions relating to good stewardship, manufacturing and environmental practices; monitoring for emerging resistance; and ensuring supply of the antimicrobial. The pilot project imposed a cap on the maximum contract value of £10m per year. The cap was set at the outset of the project and was communicated to companies before the inviting them to submit their final application to be part of the pilot. The value of £10m reflects England’s ‘fair share’ of the global pull incentive for a new antimicrobial; that is, a payment to the company that ensures a sufficient return on investment to make the development of a new antimicrobial worthwhile. It was calculated by rescaling published estimates of the required size of a global pull incentive to reflect England’s share of the pharmaceutical market.

Having a cap on the contract value set stakeholders’ expectations as to the basis on which prospective contracts would move through the procurement process from evaluation to contract awarding, and provided reassurance that the process met public contract regulations 2015 (PCR2015). Participants did suggest, however, that value of the cap would need to be reviewed in future. For example, if other countries do not pay their ‘fair share’ of a pull incentive, thereby reducing the pool of contributors, England’s contribution of £10m per year may not be sufficient to translate to a pull incentive for industry. It was noted that the NICE evaluation of both products estimated QALYs that would translate to monetary values above the cap, if quality-adjusted life years (QALYs) are valued at £20,000 each. From a public perspective, this could be seen as providing assurance that the NHS is not overpaying given the large uncertainties in the modelling. For industry, an alternative interpretation was that the companies were not fully compensated for the value of their products.

Participants argued that the cap could be flexible, varying according to how well the products met some of the selection criteria that were used to identify products eligible for the pilot. It was suggested that this would allow for more accurate reimbursement of the highest quality antimicrobials and provide incentives to companies who would otherwise struggle to qualify for the process. For instance, a lower value could be in place for products with weaker supply chain assurances, to avoid excluding small- and medium-sized companies with reduced supply infrastructure. It was also proposed that variations in value could be used to incentivise evidence generation by setting a higher value for products supported by higher quality evidence.

The contract’s surveillance requirements were supported, with recognition that this would generate data that could potentially inform future evaluations. Similar praise was given to contract’s stewardship requirements which are vital to combat antimicrobial resistance. However, there were concerns about using Blueteq forms, which are completed by doctors for approval when prescribing high cost drugs, to monitor usage because their completion is not mandatory for these pilot products. As a result, completion rates may be low and it will be difficult to monitor reasons for prescribing and adherence to the NICE guidance. Another stewardship aspect discussed in the workshops was the products’ hospital invoice price. Usage should be carefully monitored to ensure the price is not encouraging over- or under-prescribing from appropriate levels. Committee members felt that they could have provided helpful input into the price, but it was recognised that during the pilot there was not time for this to be discussed within the committee meetings. Future contracts should also consider how to account for instances of exceptional usage, during which demand increases in response to an outbreak. In extreme cases, this could mean the company would have lower revenues compared with a standard payment model.

## Eligibility and selection criteria

Products had to meet [eligibility criteria](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/Selection-Questions-Criteria-Existing.pdf) before they could be considered for inclusion in the pilot. Eligible products were then scored on a set of [selection criteria](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/award-questions-criteria-annex3.pdf). These included addressing global and UK-specific unmet clinical need (with a focus on products active against severe drug resistant gram-negative bacterial infections), product novelty and company commitments to reliability of supply and antimicrobial stewardship.

There was consensus that the pilot was correct to focus on multi-drug-resistant gram-negative infections because they present the greatest unmet clinical need for antimicrobial innovation. Participants acknowledged that a likely consequence would be to disincentivise investment in antimicrobials with characteristics outside of the selection criteria.

There are differences in global unmet needs compared with those of the UK, but participants agreed that it was appropriate to apply greater weight to the WHO pathogen priority list because support for these can be better aligned internationally to deliver a sufficient pull incentive. Participants understood that the clinical criteria used to select eligible products are likely to evolve in future as global unmet needs change, as has been the case historically. They suggested consulting with international experts to inform this. However, they cautioned that changing the selection criteria would penalise antimicrobial products taken forward through clinical development, at great expense, based on criteria that are subsequently removed by the time the product comes to market.

The other clinical selection criteria were positively regarded, and participants felt they were appropriately weighted. A few modifications were suggested. For example, the assessment of a product’s novelty should extend beyond the novelty of the chemical entity and encompass factors such a mode of delivery. Products with oral or nasal delivery systems are more sustainable than intravenous drugs and can be administered in the community, reducing length of hospital stay and the risk of in-hospital transmission of resistant infections. Clinical experts were keen to incentivise products that reduce pressure on UK hospitals.

Participants considered the non-clinical criteria to be appropriate. But they suggested that, as the process moves from competitive selection to being open to all eligible products, the non-clinical criteria would be more appropriate as key performance indicators (KPIs) in the contract rather than determining whether a product is eligible for a contract, such as assurances over the supply chain. But it was proposed that delinking sales force remuneration from sales volume should remain an eligibility criterion, and should in fact be strengthened to stipulate that companies must have already done this before entering the procurement, instead of requiring them to do so in future (as the was the case in the pilot). This would signal to companies that good stewardship practices for antimicrobials are a pre-requisite for consideration for a contract.

Participants noted that the quality and quantity of data used to determine whether products meet selection criteria is likely to be lacking. Pharmacokinetic and pharmacodynamic data were highlighted as important to determine whether antimicrobials were effective at penetrating tissue at the site of infection. The evidence requirements attached to the selection criteria were seen as crucial to act as signals to companies to improve data collection.

With the focus of the pilot evaluations on new antimicrobials, participants advocated for extending the eligibility for subscription-based reimbursement to all on-patent antimicrobials on the market. Participants noted that because the antimicrobial pipeline is currently limited, extending this payment model to older antimicrobials could accelerate the development of new ones. There was also appetite for broadening the eligibility for UK subscription-based contracts to include antibiotics outside the WHO priority pathogen list and other types of antimicrobials e.g. antifungals. A 2-tier system was suggested - with a higher cap for antibiotics that target priority pathogens, and a lower cap for antimicrobials that address a lesser unmet need.

## NICE evaluation

The NICE committee met in public in January and February 2022 and the outcome of these meetings was published as draft NICE guidance in April 2022, alongside all the documents considered by the committee. Commercial discussions between NHS England and the respective companies – informed by NICE’s draft guidance – took place in Spring 2022, the contracts were awarded in June, and the new payment structure took effect from July 2022. Final NICE guidance, updated to include details of the commercial arrangements, was published for [ceftazidime–avibactam](https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam) and [cefiderocol](https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol) in August 2022.

### Achieving the ‘pull incentive’ objective

The principal policy objective of the pilot was to provide a payment mechanism that offered an appropriate ‘pull incentive’ to prospective antimicrobial companies to invest in research and development of new products.

Support for the purpose, execution and outputs of the pilot was universal. Participants congratulated NICE and NHS England for pioneering such a clear and transparent approach that addresses a major market failure in healthcare. They were encouraged that knowledge-sharing activities with devolved nations in the UK and G20 partners are already underway to encourage international alignment and provide the necessary *global* pull incentive for industry. In particular, the US was singled out as the most important country to support this approach due to its large contribution to global healthcare expenditure.

Participants suggested that the pharmaceutical industry should be consulted to determine whether this pilot payment model actually translates into increased investment in antimicrobials. It was noted that the pilot project evaluated two very effective antimicrobials, and that not all future products will justify the same level of contract value, potentially reducing the size of the pull incentive.

Participants felt that the principal barrier to achieving a global pull incentive through this type of HTA and payment model was the complexity of evaluation. The process was resource intensive for NICE, EEPRU and the companies. Given that international co-ordination is essential to achieve a pull incentive, it is crucial for the process not to be too burdensome because some countries will not have HTA agencies as well-resourced as NICE, or might have lower levels of antimicrobial resistance and a smaller appetite for action. For these countries, participants suggested that a process using qualitative criteria to score products might be preferable to a full health economic model. This was also raised as a potential solution for the future NICE process, to accommodate the lower evidence quality in antimicrobial effectiveness research and uncertainty in health economic modelling methods.

Finally, some participants suggested that subscription-based contracts for antimicrobials should be excluded from the [voluntary scheme for branded medicines pricing and access (VPAS)](https://www.gov.uk/government/publications/voluntary-scheme-for-branded-medicines-pricing-and-access), because the repayments could undermine the pull incentive.

### Estimating the value of antimicrobials to the NHS

Estimating the full value of an antimicrobial is complex and requires a different perspective to that which NICE currently uses. NICE’s current evaluation methods focus on health benefits for people that receive the drug, and sometimes their carers. For antimicrobials, the health benefits go far beyond this. For example, effective antibiotics are essential in:

* reducing problems associated with overuse of a broad-spectrum antimicrobial by replacing it with a narrow-spectrum drug (‘spectrum value’)
* reducing the spread of infection to other people (‘transmission value’)
* ensuring that chemotherapy, surgery and other medical procedures can go ahead (‘enablement value’)
* providing a range of treatment options to reduce the risk of resistance developing and be prepared for existing antimicrobials becoming ineffective (‘diversity value’ and ‘insurance value’).

Collectively these additional attributes of value are abbreviated to ‘STEDI’ values.

The scope and scale of EEPRU’s modelling was praised by all participants, especially in light of the tight timescale within which they achieved it. Identifying and synthesizing *in vitro* susceptibility evidence and linking it to downstream health outcomes was seen as an immensely complex task that had not previously been attempted for antimicrobials. Although not all benefits were captured by the model, the outputs were perceived to be very informative and helpful by both committee members and key opinion leaders in antimicrobial resistance.

The most prominent aspects of value not fully captured by the model were STEDI (spectrum, transmission, enablement, diversity and insurance) values, which are seen as central to quantifying the additional value of antimicrobials compared with other types of therapies. Participants noted that this reflects the lack of methods and data available to model them appropriately rather than the quality of EEPRU’s work. Of the STEDI values, participants highlighted enablement and insurance value as the most important drivers of value and that methodological work in these areas should be encouraged. Others noted that some of the STEDI values, such as insurance and diversity value, overlap and would double count benefits if they were both modelled. Participants advised adapting the STEDI framework to account for this.

Participants recognised that these evaluations placed new responsibilities on the committee: they had to agree a precise number in terms of population QALYs, informed by an unusual and complex model which they felt did not capture all relevant benefits or patient groups. It is unusual for a NICE committee to assign a value to benefits not captured in a model, but it was important for informing the commercial discussions between NHS England and the companies. There was admiration and understanding for how the committee navigated these challenges. In particular, it was noted that the committee had to make recommendations in the face of considerable uncertainty, and that “the perfect should not be the enemy of the good”. Participants noted that the committee’s final QALY estimates (accounting for the uncaptured value in the model) relied on expert opinion and committee judgement. It was acknowledged that the methods and data sources for quantitatively evaluating the full value of a new antimicrobial need further refinement before it is possible to reliably, robustly and fairly replicate the process used in the pilot. Academics advised that this programme of research would take years. Participants noted that improved surveillance will help inform estimates of patient population sizes, which were an influential driver of the QALY benefits, but speculated that forecasting trends in resistant pathogens was likely to remain highly uncertain even as data collection and quality improves over time.

### Providing stewardship guidance

All participants agreed that incorporating stewardship advice into the guidance documents was appropriate and welcome, and an important part of knowledge-sharing activities with international partners.

### Using the NICE multiple technology appraisal (MTA) process

The pilot’s technology evaluation process was modelled on the NICE multiple technology appraisal (MTA) process, in which an academic group is commissioned to do the economic analyses and companies are invited to submit evidence in support of their products, including their own economic model. The academic group commissioned for the pilot was the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (‘EEPRU’). A specially convened [NICE committee](https://www.nice.org.uk/get-involved/meetings-in-public/antimicrobials-evaluation-committee) made up of existing NICE committee members, supplemented by several specialist members, was responsible for deliberating on the evidence, including EEPRU’s findings and comments received during the consultation of EEPRU’s reports, and determining the value of the products to inform commercial discussions between NHS England and the respective companies.

Participants agreed that it was appropriate to use a multiple technology appraisal (MTA) process for the pilot. As there was a lack of consensus for how to model antimicrobials, using an academic group to develop the model ensured consistency between the two evaluations. Using a large academic group meant that substantial staff and resources could be assigned to the project, which was more resource intensive and technically challenging than anticipated.

Some participants argued that greater company involvement should be introduced as the process develops. It was noted that a single technology appraisal (STA)-style process, in which companies submit their own economic model, could be more appropriate in future as a means of reducing the resource burden on NICE and the external assessment group. This view was not unanimous amongst industry, because small to medium-sized antimicrobial companies are unlikely to be able to develop economic models with the required level of complexity. Academics were also concerned about the risk of companies introducing bias into the model, which would be difficult for an academic group to identify and amend because of the complexity of the model and shorter timescales of an STA. Routine development of economic models of antimicrobials would also require explicit NICE guidance on how those models should be produced, akin to the reference cases that underpin each of NICE’s guidance-producing programmes. Participants suggested that a dedicated specialist committee could be formed so that specialist knowledge on the particulars of antimicrobial evaluations would be accumulated and retained.

The complexity of antimicrobial modelling led participants to suggest that a common model applicable to a wide range of antimicrobials could be developed. This would ensure consistency, improve robustness and avoid duplicating efforts across evaluations. An alternative suggestion was to depart from both the STA and MTA style of assessment, which both use cost-utility analyses to quantify benefits, and instead adopt a more qualitative approach that scores products on a set of criteria, which could use some of the criteria used to select the two products for the pilot. This system would be similar to that suggested in the proposed PASTEUR Act in the US and would not necessitate complex modelling. A common conceptual model could be developed, linking basic information on mode of action, *in vitro* evidence and STEDI values to obtain a contract value.

# Project team conclusions

NICE is the first HTA organisation anywhere in the world to attempt to estimate the full benefits of an antimicrobial by quantifying the population health effects through consideration of the STEDI values. This was a ground-breaking project that has provided the first quantification of the value of important antimicrobial products which target difficult-to-treat drug-resistant pathogens with a high unmet need in the UK and designated as a global priority by the WHO.

EEPRU used innovative modelling methods in these evaluations. For example, in the absence of RCT or observational data that was generalisable to multi-drug resistant infections, EEPRU used results from in vitro ‘susceptibility’ studies – which determine how well an antimicrobial slows a pathogen’s growth – as a surrogate for modelling clinical outcomes. EEPRU used a combination of expert elicitation and published evidence to link susceptibility data to relevant clinical and economic outcomes including mortality and length of hospital stay by ward type, and estimate the relative effectiveness of the products in terms of QALYs. This represents an important advance in the evaluation of antimicrobials, although EEPRU have advised that the methods need refining, which is reflected in NICE’s recommendations for research.

The approach to the pilot project was resource intensive, and it would not be possible to apply this approach routinely without significant developments in the methods for economic analysis and improved surveillance, as described in NICE’s research recommendations. This programme of research would take years. NICE are considering this feedback in the context of the following:

1. The need to develop and implement the “routine” arrangements for the evaluation and purchase of antimicrobials with minimal delay following the pilot.
2. The existing capacity constraints and finite HTA expertise available to support NICE’s technology evaluation programme.
3. NICE’s initiative to create a ‘proportionate approach’ to HTA; balancing the resource with the complexities and risks of each HTA.
4. The importance of timely NICE guidance and achieving appropriate patient access as close as possible to marketing authorisation dates for clinically important new antimicrobials.

We also heard from stakeholders at the workshops that a quantitative health economic-based process might not be appropriate for antimicrobials because the evidence base is unlike traditional effectiveness evidence for other interventions, and because there were several sources of uncertainty and uncaptured value in the economic model. The suggestion was made to use a qualitative framework with a points-based scoring system to determine the contract value for an antimicrobial, instead of using health economic modelling to estimate QALYs. This scoring system could be based on the eligibility and selection criteria used to select the two products for the pilot, and also informed by the quantitative value estimates from the pilot.

It was encouraging that the QALY estimates from the pilot evaluations are sufficient to justify paying England’s ‘fair share’ towards antimicrobial R&D. The most recent calculations of an appropriate global pull incentive ([Outterson 2021](https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.00688)) suggest that England’s £10m annual payment is a generous contribution to the global effort; sitting at the upper end of the target range models. Stakeholders have been invited to submit evidence of what they think the UK contribution should be, if they think the current maximum contract value is insufficient to deliver an appropriate pull incentive.

# Appendix 1 - Comments from workshop participants

Square brackets denote who made each comment.

## Procurement process

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Theme** | **What went well?** | **What needs improving?** | **What impact would the improvements have?** | **Key lessons** |
| Open competition approach | * Process was appropriate given that only two products could be selected for the pilot. *[Industry]* * The complexity of antimicrobial landscape meant dialogue opportunities with NICE, NHSE and DHSC were very helpful. *[Industry]* * Transparent engagement with stakeholders was very well received globally. *[Committee member]* | * Simplify process to make it less burdensome for companies. NICE process required significantly more resources than Swedish pilot, and this cause delays to launching other company products. The benefit of the Swedish model was that it was open to all eligible products and did not include a selection mechanism.Future subscription-based contracts in the UK should be available for all eligible products i.e. remove the competition for limited number of slots. *[Industry]* * Communication about evidence requirements should start as early as possible. | Process would remain commercially attractive and all eligible products would benefit from subscription-based contracts. | Necessity of procurement process was questioned but is required to meet regulations on public sector contracts. However, simplification of process would be welcomed. |

## Model contract

| **Theme** | **What went well?** | **What needs improving?** | **What impact would the improvements have?** | **Key lessons** |
| --- | --- | --- | --- | --- |
| Contract value cap | * The role of the cap in meeting public contract regulations 2015 (PCR2015), is understood as necessary. It also set industry’s expectations and mitigated the risk to the NHS budget in light of high uncertainty in value estimates. *[Industry and KOL]* * The cap accurately reflected England’s ‘fair share’ *[KOL]* * Contract (separate from the cap) was well regarded and provided an efficient means of managing the whole evaluation and reimbursement process. *[Industry]* | * The NICE evaluation of total value exceeded the £10m cap – if QALYs are valued at £20,000 each – suggesting that the cap should be increased. *[Industry]* * Not all antimicrobials deserve the £10m cap, but very good antimicrobials should get more than £10m. *[KOL and clinical expert]* * A more objective (e.g. non-industry) view from academia on appropriate level of the cap would be welcomed. *[Industry]* * The UK’s contribution of a sufficient pull incentive would be higher than our ‘fair share’ of £10m if other countries do not pay their own ‘fair share’. *[Industry]* * Variation in cap value based on how well product meets eligibility criteria would be appropriate. Could be beneficial to small to medium-sized antimicrobial companies *[KOL and Industry]* * Level of payment could also reflect the quality of evidence to incentivise improved research methods. *[Academia]* * More clarity on ‘exceptional volume’ situations would be welcome, e.g. temporary demand spikes that would have generated significant additional revenue for the company outside of a subscription-based contract. *[Industry]* * Remove the option for companies to propose a contract value below the cap. *[Industry]* * Consider publishing contract values, because if they remain confidential it might not work as a pull incentive. *[Industry]* | Reviewing and justifying the level of the cap would support the successful delivery of an appropriate pull incentive. | The cap was important to allow us to move forward with the pilot. Flexibility over the value of the cap should be considered. |
| Stewardship and surveillance requirements in the contract | * Surveillance requirements are important for generating data to estimate burden of resistant infections and value of future antimicrobials. *[Industry and KOL]* * Strong support for stewardship requirements. *[Industry]* * Sales data indicate that usage has not dramatically changed since introducing the new invoice price*. [Industry]* | * Difficult to commit to the British Society for Antimicrobial Chemotherapy (BSAC)’s UK antimicrobial registry at the contractual phase because the registry’s requirements were yet to be finalised. *[Industry]* * Using Blueteq forms to monitor usage will be difficult because they are not mandatory. *[Committee member and Industry]* * Committee should have a bigger role in setting the hospital invoice price. Unintended stewardship consequences of current price should be carefully monitored. *[Committee member, KOL and Industry]* * Learnings from pilot can be used to inform what type of surveillance studies would be most useful for modelling. *[Academia]* * We shouldn’t rely on price to enact good stewardship. *[Academia]* | Good stewardship and surveillance mitigates against increased resistance to a new antimicrobial.  Surveillance can help inform future assessment of antimicrobial value. | More committee time would have been helpful to inform appropriate invoice prices.  The Blueteq form should be promoted and encouraged. However it might not be the best surveillance mechanism because it isn’t mandatory. Completion rates to be monitored by NHS England. |

## Eligibility and selection criteria

| **Theme** | **What went well?** | **What needs improving?** | **What impact would the improvements have?** | **Key lessons** |
| --- | --- | --- | --- | --- |
| Selecting the ‘right’ products | * By evaluating two drugs for severe multi-drug resistant gram-negative infections, the pilot has incentivised R&D in the right areas - those with high global unmet need. This focus on global priorities, rather than solely the UK’s unmet need, is needed to generate sufficient revenues for a successful pull incentive. *[Committee member, KOL, Academia and Industry]* * Unmet needs for the UK were also well-reflected. *[Industry]* * Products addressing carbapenem-resistance is a critical clinical issue so it was appropriate to focus on these in the selection criteria. *[Committee member]* * Selection criteria were broadly appropriate and it was important to reflect non-clinical as well as clinical factors. *[Committee member and Industry]* * Criteria were appropriately weighted (in favour of clinical criteria, mainly unmet need). *[Committee member and Industry]* * Process for selecting criteria was justified but may change based on context of experts consulted. *[Committee member]* | * International expertise should be sought when agreeing future eligibility criteria, to ensure we continue to reflect global unmet needs. *[KOL and Clinical expert]* * Criteria will need to be updated in the future as in global unmet needs change. But being mindful that frequent changes to the selection criteria would penalise antimicrobials currently in clinical development for a clinical need that is subsequently deprioritised. *[Industry and Clinical expert]* * Criteria should reward products that address challenges to the UK NHS (but weighted to prioritise global needs over UK needs), which includes: shortening hospital length of stay, reduced dosing frequency, shorter duration of treatment, oral instead of IV, less drug interactions and adverse events. These are also relevant for low and middle income countries, especially dosing frequency and duration of treatment. *[Clinical expert, academia and committee member]* * Eligibility for subscription-based contracts should be broadened to include: older antimicrobials already on the market, antibiotics outside the WHO priority pathogen list (e.g. antibiotics for gram-positive infection), other types of antimicrobials (e.g. antifungals). The maximum contract value (cap) could vary for different categories of antimicrobial e.g. a 2-tier system with a higher cap for new-to-market antibiotics that target priority pathogens, and a lower cap for antimicrobials that address a lesser unmet need. *[Industry, KOL, Clinical expert and Academia]* * Eligibility could reward products licensed in children, to incentivise early data collection. *[Academia and Clinical expert]* * Weighting should be changed to reward novel mechanism of action and innovation. *[KOL]* * Novelty of the chemical entity is a highly aspirational criterion that is difficult to meet. Assessment of novelty should include other aspects e.g. mode of delivery - oral/nasal delivery could reduce hospital pressure and be more sustainable. However, stewardship challenges increase with increased ease of use. *[Industry, Clinical expert and Committee member]* * Need better quality evidence to determine whether products meet selection criteria. For example, PK/PD data on tissue penetration is crucial to determine whether antimicrobials reach site of infection. *[Committee member and Industry]* * Pre-requisite for selection should be a sales force which already has its renumeration delinked from product sales (rather than asking companies to commit to this in the future, as in the pilot selection criteria). This would reward good stewardship and discourage overprescribing. *[Committee member]* * Unnecessary to include selection criteria that are also part of the contract’s key performance indicators, such as assurances over the supply chain. Although note that small to medium-sized antimicrobial companies will have less capability to meet to criteria such as these. *[Industry]* | Focus on global needs, rather than solely those of the UK, is needed to generate sufficient revenues for a successful pull incentive.  Selecting products with different modes of administration could provide substantial benefits to health system and reduce in-hospital transmission of resistant pathogens.  Broadening the entry criteria (e.g. to include antibiotics for gram positive bacteria and antifungals) would allow more companies to qualify for the process and incentivise antimicrobial innovation. | Criteria for the routine evaluation framework should be updated to reflect other important elements of value, prioritising global unmet needs over local ones (without ignoring benefits to the UK NHS). Criteria will need periodically updating to reflect changes in global unmet needs. But with careful consideration of the impact on antimicrobials in development. |

## NICE evaluation

| **Theme** | **What went well?** | **What needs improving?** | **What impact would the improvements have?** | **Key lessons** |
| --- | --- | --- | --- | --- |
| Achieving policy objectives - creating a pull incentive | * The successful commercial negotiations have put the project forward as an international example of how to address market failures of antimicrobials. *[Committee member, Clinical expert, KOL and Academia]* * Knowledge-sharing initiatives with the UK devolved governments, US and other countries have begun and will continue. *[Industry, Academia and Clinical expert]* * Empirical evidence suggests that creating these kinds of incentives will stimulate innovation. *[KOL]* * The process was very transparent, with clear assessment criteria. *[Academia]* | * Whether the specific pull incentive from this project is sufficient will depend on industry response (with respect to investment in antimicrobials and product launches in the UK). Industry could be surveyed about this. *[Industry, KOL and Committee member]* * The two products evaluated in the pilot are likely the ‘lowest hanging fruit’, so future contract values may be lower and not reflect a sufficient pull incentive. *[Industry, KOL and Committee member]* * Complexity of the evaluation could be a barrier to other countries replicating process. A more qualitative framework, similar to the points-based scoring system used for selecting the products for the pilot, could be more appropriate and transferable to other countries. *[Industry and KOL]* * Low levels of resistance in European countries might deter them from providing ‘fair share’ of pull incentive. Communication of global unmet needs is crucial for objectives to be met. *[KOL]* * A new model for evaluating and reimbursing microbial diagnostics is needed. Also need better evidence for diagnostics – studies don’t usually show benefits for mortality or clinical outcomes because of study design. *[Academia, Clinical expert, KOL and Committee member]* * Subscription-based antimicrobial contracts should be excluded from the voluntary scheme for branded medicines pricing and access (VPAS). *[Industry]* | Support the delivery of an appropriate pull incentive and encourage innovation globally. | The pilot has global significance in the fight against antimicrobial resistance. Evaluating its success will take time because it is dependent on international co-operation to jointly provide a large enough incentive for industry to increase investment in antimicrobial R&D. |
| Estimating the value of the antimicrobials to the NHS and recognising the additional benefits not normally considered by NICE (‘STEDI’ values) | * EEPRU did an impressive job in modelling a very complex problem with substantial gaps in data. Although some benefits could not be captured by the model, it was ultimately useful and set the committee on the right path. *[Industry, KOL and Committee member]* * The committee’s recognition of missing patient groups and uncaptured value was welcome given the limitations of the modelling. Reaching a value estimate was challenging but a success. *[Committee member and Industry]* * Appropriate for committee to attempt to estimate the size of the uncaptured benefits despite the uncertainty, because of the importance of this project – and innovative approaches in other countries – in tackling antimicrobial resistance. Should not let the perfect be the enemy of the good. *[KOL]* * Helpful to have intensive care unit clinicians and other experts on hand during committee discussions. Notable that all clinicians agreed on the value of the products. *[Committee member]* | * HTA-style process might not be appropriate for antimicrobials because the evidence base is unlike traditional effectiveness evidence for other interventions (e.g. clinical trials are all non-inferiority and treatment is likely to be pathogen-directed), and there were several other sources of uncertainty and uncaptured value in the economic model. Instead of using health economic modelling and QALY estimates, the contract value could instead be determined using a scoring system based on the eligibility and selection criteria used to select the two products for the pilot. *[Industry and KOL]* * EEPRU was unable to fully model the STEDI values. It’s particularly important to capture enablement and insurance value. *[KOL, Committee member, Patient expert and Industry]* * EEPRU’s population-level QALY estimates were sensitive to population size, where value increased with increased usage, which contradicts theory of insurance value and undermines good stewardship; another reason that traditional HTA-style process might not be appropriate for antimicrobials. *[Committee member]* * Forecasting trends in resistance will likely remain difficult even as more and better data become available. Population size can be more accurately measured using improved surveillance data. *[Industry]* * A wider range of adverse events (in addition to acute kidney injury) should be accounted for (e.g. ototoxicity) *[Committee member]* * Future approach must mitigate the risk of double counting safety and other aspects of value when estimating STEDI values. *[Committee member]* * Estimating the value of the optimal stewardship scenario requires most accurate estimate of who *should* be receiving drug in practice, but there are no data on this. *[Academia]* * Paying a minimum of 60% of overall value to company during contract is an underestimate. It is more likely 70-80% for non-antimicrobial products. *[Industry]* | Using qualitative criteria and a points-based scoring system might be more appropriate than QALY estimation and would be significantly less resource intensive.  A replicable approach that can be routinely applied to eligible antimicrobials will ensure consistency, fairness and transparency in committee’s decision-making and the final contract values. | Despite uncertainty in the precise estimate of value, the QALY gains are sufficient to justify paying England’s ‘fair share’ towards antimicrobial R&D. But the QALY estimates relied on committee judgement. More applied and methodological research and improved antimicrobial surveillance – as described in NICE’s research recommendations – is required before we can robustly and fairly replicate the process of using formal economic analysis to quantitatively estimate QALYs. So an HTA-style process might not be appropriate for antimicrobials. |
| Providing stewardship guidance | * Guidance on stewardship was appropriate and welcome. *[Clinical expert and Industry]* | * Important that stewardship principles are passed on as other countries take up similar schemes. *[Industry]* * De-escalation strategies of switching away from ‘last resort’ antimicrobials when lab results are available are also important. These may not be appropriate for these particular pieces of guidance. *[Academia and Clinical expert]* | Ensuring the value of the antimicrobials is maintained in practice and reducing the risk of resistance. | Content and scope of stewardship recommendations is not exhaustive but likely appropriate for this type of NICE evaluation. |
| Modelling the process on the NICE MTA process | * Appropriate for an academic group to develop the model for the pilot to ensure consistency across the 2 evaluations, given the lack of consensus in methods and risk of bias, and use EEPRU’s existing expertise. *[Committee member, Clinical expert, KOL and academia]* * Using a large academic group meant that substantial staff and resources could be assigned to the project, which was more resource intensive and technically challenging than anticipated. *[academia]* | * The company should have a bigger role in developing the health economic model that informs committee decision, once the methods for economic analysis of antimicrobials have developed. This would require clear guidance from NICE on its requirements, including a bespoke reference case, and a dedicated antimicrobials committee. *[Committee member and Industry]* * Producing a common economic model (ie not product specific) would mean not having to replicate EEPRU efforts every time and ensure consistency across evaluations. It should include standardised techniques for analysing relevant datasets (e.g. UKHSA and other surveillance data) and synthesising evidence, and agreement on the most appropriate data sources. *[Academia, Committee member, KOL and Industry]* * NICE could use a more pragmatic approach to evaluation instead of estimating QALYs using an economic model. For example, a points-based scoring system similar to the pilot’s eligibility and selection criteria. We could learn from the proposed system in the USA (the PASTEUR act). This would still require a framework to convert points into a contract value. *[KOL, Committee member and Industry]* * Mechanism for company to appeal decision is missing *[Industry]* | If replicating the QALY-based approach, efficiency could be achieved either by greater company input or a generic economic model that could be used for any antimicrobial. | The pilot was highly resource intensive and it wouldn’t be feasible to replicate this for every antimicrobial evaluation. There are different ways of achieving efficiencies in the process that would shift burden away from academic groups, including a more pragmatic approach which uses a points system rather than estimating QALYs. |

# Appendix 2 - Verbatim questions presented at the workshop

**Procurement process**

* What are your thoughts on the procurement process used for the pilot?
* Should these elements be retained in the future routine approach?
* If changes are needed, how should the process be amended?

**Model contract**

* What are your thoughts on the contract design used for the pilot?
* Which elements should be retained in the future routine approach?
* Which elements need amending?

**Criteria for selecting the 2 products in the pilot**

* What are your thoughts on the selection criteria used for the pilot?
* Do the criteria need amending for the future routine approach?

**Achieving policy objectives**

* Does the design of the pilot deliver the intended pull incentive?
* How could the design be amended to better achieve a pull incentive?

**Estimating the value of antimicrobials to the NHS**

* What are your thoughts on committee’s approach to estimating uncaptured value?
* What are the most important attributes of value to capture? Quantitatively or qualitatively?

**Stewardship guidance**

* What are your thoughts on the approach to deriving the stewardship recommendations?
* How could the approach to developing stewardship recommendations be improved?

**Modelling the process on the NICE MTA process**

* Was it appropriate to commission the model to an academic group (rather than being company-led)?
* Were there sufficient opportunities and time for company and other stakeholder input?
* Is the approach used in these evaluations scalable and sustainable?