Key issues for committee discussion

Table 1 summarises the key issues for committee discussion. Additional context and cross-references to committee papers are provided in the prose below the table. Questions which are likely to have the greatest impact on QALY estimates have been designated “high priority” and are marked in bold in table 1.

This document has been prepared for the cefiderocol evaluation. It was adapted from the one prepared for the CAZ-AVI evaluation to include additional issues relevant only to cefiderocol, and to update the cross-references to the cefiderocol committee papers.

**Table 1: Summary of key issues**

| **Category** | **Issue** | **Form of judgement** | **Effect on committee conclusions** |
| --- | --- | --- | --- |
| Potential uncaptured value: missing patient groups | **Key issue 1:** **Have patients who are likely to benefit from cefiderocol been excluded from the analysis?** | That there is additional benefit that can be quantified, and in a form that can be used to modify committee’s QALY estimate.  +  That there is further additional benefit that can be quantified, but not in a form that can be applied to committee’s QALY estimate. | Adjust committee’s quantitative estimate of overall incremental value.  +  Supplement the overall QALY estimate with the additional numerical estimate of uncaptured value. |
| Potential uncaptured value: incremental benefit in patients outside the ‘High Value Clinical Scenarios’ | Key issue 2: Is the magnitude of benefit in the high value clinical scenarios generalisable to wider expected usage? | That there is additional benefit/harm that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: Insurance value | **Key issue 3: Has insurance value been fully quantified?**  Note: Additional analyses to be made available by EEPRU. | That there is additional benefit that can be quantified, and in a form that can be used to modify committee’s QALY estimate. | Adjust committee’s quantitative estimate of overall incremental value. |
| Potential uncaptured value: Enablement value | **Key issue 4: Are there uncaptured benefits related to the ability to keep wards open during an outbreak?** | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: Enablement value | **Key issue 5: Are there uncaptured benefits related to increasing the number of procedures that can go ahead following successful treatment?** | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: transmission value | Key issue 6: Is cefiderocol expected to completely eradicate colonisation in the gut? | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: transmission value | Key issue 7: Is transmission value a significant driver of population incremental benefits or not? | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: transmission value | Key issue 8: Is cefiderocollikely to impact on the likelihood of an outbreak and its spread? | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Potential uncaptured value: diversity and spectrum value | Key issue 9: Is there uncaptured value related to diversity and spectrum value | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Estimating population size | **Key issue 10: What is the size of the baseline patient population (clinical expert versus PHE classification)?** | A preference for one parameter estimate over another. | Select committee’s preferred approach – this will affect the QALY estimate(s). |
| Estimating population size | **Key issue 11: How does the patient population grow over time (persistent growth, short-term/’damped trend’ or no growth)?** | A preference for one modelling approach over another. | Select committee’s preferred approach – this will affect the QALY estimate(s). |
| Estimating population size | Key issue 12: Is it reasonable to assume no growth in the eligible *Pseudomonas* *aeruginosa* population over time? | That there is additional benefit that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Estimating population size | **Key issue 13: How much will resistance to cefiderocolincrease over 20 years?** | A preference for one parameter estimate over another. | Select committee’s preferred approach – this will affect the QALY estimate(s). |
| Relative effectiveness | Key issue 14: Which network of susceptibility evidence should be used? | Preference for one modelling approach over another. | Select committee’s preferred approach – this will affect the QALY estimate(s). |
| Relative effectiveness | Key issue 15: Are the estimates of susceptibility to cefiderocol, relative to colistin, likely to be accurate? | That there is additional benefit or uncaptured uncertainty that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Relative effectiveness | Key issue 16: Is the relationship between susceptibility and outcomes likely to be constant across all antimicrobials? | That there is additional benefit/harm that can only be expressed in qualitative terms. | No effect on quantitative estimate of overall incremental value. Narrative output only. |
| Model assumptions | **Key issue 17: which patients should be classed as being at high risk of having a multi-drug-resistant pathogen?** | Recommendations for how the antimicrobial should be used. | Narrative recommendation. |
| Model assumptions | Key issue 18: Are the estimates of the proportion of patients in the empiric setting correctly identified as having the suspected resistant pathogen likely to be accurate, or under/over-estimated? | That there is ‘captured uncertainty’. | Quantitative estimate of overall incremental value expressed as a range, to capture uncertainty. |
| Research recommendations | Key issue 19: Could further data collection help to reduce areas of uncertainty in the QALY estimates. | Recommendations for further data collection. | Narrative recommendations. |
| Comparators | Key issue 20: Do the comparators reflect NHS practice? | Recommendations on how the antimicrobial should be used. | Identification of any inappropriate or important missing comparators. Narrative output only. |
| Contract value | **Key issue 21: What proportion of the drug’s total value over the 20-year modelled time horizon should be assigned to the potential 10-year contract period.** | Consideration of policy aims. | Proportion of value that should be assigned to the contract period. |

# Potential uncaptured value: missing patient groups and uncertainty in population size

1. **High priority:** Are there groups of patients which have been excluded from the analysis, who are likely to benefit from the intervention compared with current treatment options?
   * **Context:** EEPRU noted that there may be areas of wider usage not reflected in its analysis. This has also been noted in the manufacturers’ consultation comments. Shionogi note that a number of other MBL pathogens are relevant to the assessment (eg *Acinetobacter*, *Serratia*, *Burkholderia,* *Serratia, Burkholderia, Proteus, Providencia, Morganella* and *Achromobacter*). They suggest other infection sites should be included, noting that 15% of the early use of cefiderocol has been in bone & joint infections. Shionogi also disagreed with EEPRU’s assumption that 85% of *Stenotrophomas* infections would not be eligible to receive cefiderocol. EEPRU consider the main areas of additional usage are in people with cystic fibrosis, compromised immune systems (e.g., haematology, transplant), burn injuries, and renal complications. EEPRU noted that infections in these patient groups have been reflected in their analysis to the extent that they are caused by the pathogens and infection sites modelled (HAP/VAP, cUTI, IAI and BSI caused by MBL-producing *Enterobacterales*, *Pseudomonas aeruginosa and Stenotrophomas*). The question is, therefore, whether there are infections within these patient groups caused by different pathogens and/or presenting at different sites where cefiderocol offers health benefits over existing therapies. Note also that the proportion of patients not captured may differ depending on whether the PHE or clinical adviser classification of samples is used. EEPRU is currently working on additional analysis modelling usage in patients for whom colistin isn’t a treatment option. There may still be important patient populations who have not been captured in EEPRU’s QALY estimates.
   * **Why it matters:** If patients have been excluded from the analysis the full population incremental net health benefit may not have been captured.
   * **Cross-references to committee papers for cefiderocol:** The population included in the high value clinical scenarios is described in the Assessment Report, Section 4.2.4 and 8.2.1.1. The population included in wider expected usage is described in the Assessment Report, Section 8.2.6.3.

# Potential uncaptured value: incremental benefits in populations outside high value clinical scenarios

1. **High priority:** Is the magnitude of incremental health benefit in the high value clinical scenarios generalisable to wider expected usage?
   * **Context:** Estimating the benefit of cefiderocolacross its full expected usage relies on the assumption that incremental net health benefits (QALY gains) are the same in the additional populations, which weren’t included in the patient level model, as in the high value clinical scenarios.
   * **Why it matters:** This is a strong assumption. Committee will need to consider whether (on average) the QALY gains for patients in the wider expected usage or excluded populations are the same, larger or smaller than in the high value clinical scenarios.
   * **Cross-references to committee papers for cefiderocol:** Methods for extrapolating results to wider expected usage are described in the Assessment Report, Section 8.2.6.

# Potential uncaptured value: additional attributes of value (‘STEDI’ values)

**Context and why it matters:** Key issues 3-9 cover additional attributes of value specific to antimicrobials (the ‘STEDI’ values). Not all the ‘STEDI’ elements of value have been fully modelled by EEPRU, either because they weren’t considered to be significant drivers of incremental population benefits, or because there was insufficient evidence or uncertainties in the data. Because the aim of this evaluation and delinked payment model is to incentivise the market by recognising the full value of antimicrobials, it is important for committee to determine whether there is uncaptured value and the likely magnitude of any uncaptured benefits. Consideration of potential uncaptured value should be specific to the benefits generated by the antimicrobials under evaluation, as opposed to how any antimicrobial could, in principle, provide value.

# Potential uncaptured value: insurance value

1. **High priority:** Has insurance value been fully quantified?
   * **Context:** Insurancevaluehas beencaptured in the model byreflecting low levels of resistance emergence to cefiderocoland growth in the numbers of infections within the high value clinical scenarios and other areas of expected usage over 20 years. Restricting usage of cefiderocolpreserves its efficacy in the long term, meaning that health benefits accrue in future cohorts of patients.However, there may be scenarios where insurance value has not been captured. These include:
     1. Higher levels of resistance to existing drugs within the areas of expected usage over time
     2. The emergence of multi-drug resistant pathogens against which CAZ-AVI/cefiderocol is effective that are currently rare or even unknown.
     3. Pathogens that are currently treatable with existing therapies becoming resistant to those treatments, but susceptible to CAZ-AVI/cefiderocol.

In response to committee feedback, EEPRU performed additional scenario analyses which model increased resistance to current treatments, including catastrophic scenarios where high levels of resistance emerge, to estimate QALY gains should such scenarios occur.

Note that EEPRU’s analysis assesses the value of a specific, restrictive stewardship, usage scenario. It does not compare the value of this restrictive scenario with higher usage scenarios, because this would have required a different model structure, which includes the relationship between usage and resistance emergence.

* + **Cross-references to committee papers for cefiderocol:** Insurance value is examined in the Assessment Report, Section 9.3.2.3. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45. The results of EEPRU’s additional analyses are provided in an addendum to their report (addendum 1).

# Potential uncaptured value: enablement value

1. **High priority:** Does committee agree with EEPRU’s conclusion that the ability to keep wards open during an outbreak is unlikely to be a significant driver of population **incremental** benefits with cefiderocol? If not, what is the likely magnitude of any uncaptured benefits?
   * **Context:** Hospital wards may be closed during an outbreak of a multi-drug resistant infection,to prevent transmission to other patients. Wards may also be closed as a result of only one patient being infected. EEPRU considered it unlikely that cefiderocolwill increase the likelihood of keeping wards open compared to existing antimicrobials, because most patients have alternative treatment options available. Note this aspect of enablement value overlaps with other elements which **have** been quantified in EEPRU’s model. That is, the benefits of reduced use of hospital resources leading to enablement of procedures and health care for other patients.
   * **Cross-references to committee papers for cefiderocol:** Enablement value is examined in the Assessment Report, Section 9.3.2.1. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45.
2. **High priority:** What is the likely magnitude of the aspects of enablement value that EEPRU considered to be potential drivers of incremental benefits, but were unable to model because of uncertainty in the data?
   * **Context**: EEPRU considered the following aspects of enablement value to be potentially important, but could not quantify the impact:
     1. Increasing number of procedures that can go ahead, in patients for whom existing antimicrobials are not an option due to tolerability issues (e.g., myeloma patients with renal impairment could not be treated with colistin) or are not effective (e.g., cystic fibrosis patients who have been removed from lung transplant list, who are made well enough through treatment with new antimicrobial) – not quantified.
     2. Improved treatment of pre-operative infections - partially quantified. While this usage is included within the HVCS and wider usage populations the model assumes that all patients who are alive after 30 days experience the same survival. If, however, the speed of resolution of an infection influences whether a procedure or treatment can go ahead, then it is possible that 30 day survival is longer for patients whose infection resolves more quickly as they may be more likely to receive procedures. Consultation comments from Shionogi indicate that they consider that this aspect of enablement value has not been captured.
   * **Cross-references to committee papers for cefiderocol:** Enablement value is examined in the Assessment Report, Section 9.3.2.1. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45. See Shionogi’s consultation comments on the Assessment report: numbers 64 and 65.

# Potential uncaptured value: transmission value

1. Is cefiderocolexpected to completely eradicate colonisation in the gut?
   * **Context:** EEPRU’s model assumesthat when an infection is considered clinically resolved, the pathogen may not be fully eradicated from the gut. Where use of cefiderocolreduces mortality, it will increase the number of people returning to the community, and therefore increase the risk of patients introducing a resistant strain in the wider community if colonisation is not eradicated.
   * **Why it matters:** If pathogens are completely eradicated this will have a positive effect on transmission value, as it will prevent resistant strains being spread to the community.
   * **Cross-references to committee papers for cefiderocol:** Transmission value is examined in the Assessment Report, Section 9.3.2.4. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45.
2. Does committee agree with EEPRU’s conclusion that transmission value is unlikely to be a significant driver of population **incremental** benefits? If not, what is the likely magnitude of any uncaptured benefits?
   * **Context:** EEPRU’s model assumes that cefiderocolhas neither a positive nor negative impact on transmission rates because of countervailing effects: if the antimicrobial reduces time in hospital this is expected to reduce transmission, but the antimicrobial could also increase time spent in hospital (thus increasing the risk of transmission) by reducing mortality in patients with poor prognosis. Cefiderocolcould also lead to transmission in the community if it is assumed that treatment does not completely eradicate gut colonisation (see question above). Cefiderocolreduced hospital length of stay by of 0–1.1 days, and increased length of life by up to 33 days. Patients are also likely to be re-admitted to hospital after discharge, but this were not quantified.
   * **Cross-references to committee papers for cefiderocol:** Transmission value is examined in the Assessment Report, Section 9.3.2.4. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45.
3. Is cefiderocol likely to impact on the likelihood of an outbreak and its spread?
   * **Context:** EEPRU’s clinical advisors discussed the substantial impact of outbreaks of multi-drug resistant infections in terms of disrupting healthcare provision and incurring large costs due to the need for more extensive infection control measures. However, no evidence was provided that cefiderocol would substantially impact on the likelihood of an outbreak or its spread.
   * **Cross-references to committee papers for cefiderocol:** Transmission value is examined in the Assessment Report, Section 9.3.2.4. EEPRU’s assessment of the importance of additional elements of value and whether it has been quantified is summarised in section 9.3.3, table 45.

# Potential uncaptured value: diversity and spectrum value

1. Is there uncaptured value related to diversity and spectrum value?
   * **Context:** EEPRU have concluded that diversity value and spectrum value are unlikely to be significant drivers of population incremental net health benefits. Pfizer and Shionogi’s responses to consultation both indicate that there may be benefits related to diversity value because new antimicrobials reduce use of existing antimicrobials, therefore prolonging their efficacy. Shionogi also identified potential spectrum value for cefiderocol due to its minimal/reduced impact on gut microbiota.
   * **Cross-references to committee papers for cefiderocol:** See EEPRU’s assessment report sections 9.3.2.2 (diversity value), 9.3.2.5 (spectrum value) and table 45 (summary). See Pfizer’s consultation response section 1.3 and Shionogi’s consultation comments on the Assessment report: numbers 66 and 69.

# Estimating population size

1. **High priority:** Is the true size of the patient population currently eligible for treatment (the ‘baseline population’ in the model) closer to estimates using PHE’s categorisation (conservative) or the clinical advisors’ categorisation (which results in higher estimates of population size)?
   * **Context:** EEPRU used 2 different approaches to estimating current infection numbers, based on different methods to classify infections from clinical specimen site: a more conservative definition provided by PHE and a broader definition provided by EEPRU’s clinical advisors. EEPRU’s clinical advisors consider PHE’s classification to underestimate the size of the eligible patient population, because it uses a narrow range of samples and relies on SGSS data which may not include patients who would be expected to benefit from treatment. For example, clinical advisers have indicated that certain units (eg cystic fibrosis units) may not always submit data to SGSS. Additionally, consultees have indicated that SGSS data may underestimate infection numbers for a range of reasons (not all hospitals have microbiology labs, and some provide incomplete data). The clinical advisors’ classification may result in overestimates, for example by including sputum samples, which may not be evidence of clinical infection. Both classifications cover a subset of the full population allowed in the marketing authorisation.
   * **Why it matters**: Population size is key a driver of QALY gain in the model, and differences are compounded as population grows over time. For cefiderocol the estimated baseline population size is 606 using the PHE classification and 1,280 using the clinical advisor classification. When applying EEPRU’s most optimistic base case assumptions in relation to QALY gains (that is, assuming persistent population growth and only a 1% increase in resistance to cefiderocol over 20 years) the total incremental QALYs with cefiderocol are 1,625 using the PHE classification and 3,559 using the clinical advisor classification.
   * **Cross-references to committee papers for cefiderocol:** Estimation of current population size discussed in the Assessment Report, Section 8.2.6.3. The impact of choice of baseline population on net health effects is illustrated in table 11 in Addendum 2 to the EEPRU report. See Shionogi’s consultation comments on the Assessment report: number 51.
2. **High priority:** Is growth in the eligible population mostly in the short term (‘damped trend’) or will it persist over time?
   * **Context:** For 1 of the pathogens modelled (*Enterobacterales*) EEPRU explored the impact of 2 alternative approaches to forecasting increases in infections over time, based on whether trends observed in historical data continue indefinitely into the future (‘persistent growth’) or not (‘damped trend’). This has a substantial effect on the population size over the modelled time horizon: when applying a damped trend model, the total population eligible for cefiderocol (across all 3 pathogens in the analysis) increased from 605-1,280 in year 1 to 1,175-2,269 in year 20. Using the persistent growth model resulted in a substantially greater increase in population size by year 20, to 2,553-4,508 patients (across all 3 pathogens in the analysis). EEPRU note that while there is little statistical or visual reason to choose one particular forecasting approach, there are reasons to favour the damped-trend model:
     1. empirical evidence from literature shows that long-term forecasts from models with damped trend generally outperform similar models without damped trend
     2. continual improvements to antimicrobial stewardship strategies may lead to reduced rate of resistance gain.
   * **Why it matters**: Population size is a key driver of QALY gains. When assuming persistent growth, the incremental QALY gains with cefiderocol double compared to QALY gains using the damped trend model. For example, when applying EEPRU’s most optimistic base case assumptions in relation to QALY gains (that is, using the clinical advisor classification of infection sites and assuming only a 1% increase in resistance to cefiderocol over 20 years) the incremental QALY gain with cefiderocol increases from 2,499 when assuming a damped trend model, to 3,559 when persistent growth is assumed.
   * **Cross-references to committee papers for** **cefiderocol:** This issue is primarily discussed in the Assessment Report, Section 8.2.5.1. The impact of quantitative extrapolation on population size is illustrated in Figure 15 and Table 33, and on net health effects in Figure 6 and Table 11 in Addendum 2 to the EEPRU report. Supporting notes and citations to literature references are provided in Appendix 15.
3. Is it reasonable to assume no growth in the eligible *Pseudomonas aeruginosa* population over time?
   * **Context:** As explained in key issue 11, EEPRU explored the impact of2 alternative approaches to forecasting increases in infections for *Enterobacterales* (damped trend and persistent growth). For *Pseudomonas,* EEPRU assumed the population size remained constant over the 20-year modelled time horizon. This is because the model with no trend gave the best statistical fit, compared with the damped trend and persistent growth models.
   * **Why it matters**: Population size is a key driver of QALY gains. EEPRU did not present the incremental QALY gains with cefiderocol when applying the damped trend or resistant growth models to *Pseudomonas* *aeruginosa*.
   * **Cross-references to committee papers for cefiderocol:** Assessment Report, Section 8.2.5.1.
4. **High priority:** What is the likely increase in resistance to cefiderocol due to the modelled resistance mechanisms over the 20-year time horizon? 1%, 5%, 10% or 30%?
   * **Context:** It is challenging to predict how resistance to cefiderocol might change over the time horizon of the evaluation because of the wide variety of factors which may affect resistance rates. Therefore, the resistance rate used is a substantial source of uncertainty.
   * **Why it matters**: Increases in resistance will reduce the clinical effectiveness of the new antimicrobial, therefore reduce the population level QALY gain. For example, in one of the base case scenarios for cefiderocol the QALY gains range from 1,291 when assuming the highest increase in resistance (30%), to 1,625 when assuming the lowest increase in resistance (1%).
   * **Cross-references to committee papers for cefiderocol:** This issue is primarily discussed in the Assessment Report, Section 8.2.5.3. The impact of choice of resistance rate on net health effects in Figure 5 and Table 11 in Addendum 2 to the EEPRU report. Supporting notes and citations to literature references are provided inand A15.3.

# Relative effectiveness: susceptibility data

1. Which network of susceptibility evidence should be used to estimate relative effectiveness (EUCAST, CLSI or both)?
   * **Context:** There are several sources of susceptibility evidence that can be used to inform the network meta-analysis (NMA) that EEPRU used to estimate the relative effectiveness of CAZ-AVI and cefiderocol. These sources use different methods to assess a pathogen’s susceptibility to antimicrobials, for example using either the clinical breakpoints set by EUCAST (Europe) or those set by CLSI (US). EEPRU’s base case economic model included only the data sources using EUCAST breakpoints, because EEPRU considered EUCAST methodology to be most relevant to UK clinical practice and they considered it inappropriate to combine EUCAST and CLSI data. Shionogi’s consultation comments suggest that even though EUCAST and CLSI have different breakpoints, their laboratory methods are comparable which means EUCAST breakpoints can be applied to data generated by CLSI laboratory methods and vice versa. By contrast, consultation comments from BSAC/RCPath suggest they are not comparable, noting that it is important the laboratories using EUCAST methods interpret results using EUCAST breakpoints and that laboratories using a CLSI methods interpret results using CLSI breakpoints, because breakpoints are calibrated for the method used. Scenario analyses were conducted using different data sources and these result in different susceptibilities. For example, for cefiderocol in Enterobacterales: using data based on EUCAST breakpoints and CLSI laboratory methods, cefiderocol was associated with a lower (not statistically significant) susceptibility relative to colistin (OR 0.32, 95% CrI: 0.04 to 2.47). Using data based on CLSI breakpoints and CLSI laboratory methods, cefiderocol was associated with a higher (not statistically significant) susceptibility relative to colistin (OR 1.38, 95% CrI: 0.16 to 12.05).

Shionogi’s consultation comments also suggested that fosfomycin studies should be excluded from the NMA because their methods aren’t relevant, robust or comparable with studies of other drugs, also noting that fosfomycin is not a relevant comparator (expect in urinary tract infections). EEPRU’s scenario analysis using only PHE data excludes fosfomycin, but both EEPRU and Shionogi consider that the limitations of PHE data mean it should not be used in isolation.

* + **Why it matters:** The base case NMA showed not much difference or poorer susceptibility of pathogens to the new antimicrobials (susceptibility to cefiderocol is lower than colistin), and therefore the benefits of cefiderocol in the patient-level model is driven by improved safety. Using different sources of evidence improves the relative effectiveness of the new antimicrobials and therefore increases the incremental net health benefits associated with cefiderocol.
  + **Cross-references to committee papers for cefiderocol:** Susceptibility data is reviewed in the Assessment Report, Section 5.2.3. The NMA is described in sections 5.5.2 to 5.5.4, with further detail in Appendix 7. The results from the NMA used in the model are described in the Assessment Report, Section 5.5.4.1. The absolute susceptibility values derived from the NMAs are detailed in the Assessment Report, Section 8.2.3.2, tables 18 and 20. See also Shionogi’s consultation comments on the Assessment report: numbers 5 and 9.

1. Are the estimates of susceptibility to cefiderocol, relative to colistin, likely to be accurate?
   * **Context:** Shionogi’s consultation comments on the Assessment Report suggest that EEPRU have underestimated the relative effectiveness of CAZ-AVI and cefiderocol, because the susceptibility data used in EEPRU’s NMA may not reflect current practice. Shionogi noted that CLSI have updated their breakpoints to remove the ‘susceptible’ category for colistin monotherapy, and EUCAST are consulting on a similar proposal. This reflects recommendations from CLSI and EUCAST that colistin monotherapy should not be used for systemic infections outside the urinary tract because it doesn’t reach adequate tissue concentrations to inhibit bacterial growth. Shionogi suggest that all isolates considered as susceptible to colistin in EEPRU’s analysis should be re-grouped with resistant isolates. EEPRU responded that their analysis used historical breakpoints on the advice of Public Health England, because it may not be possible to apply 2021 methods to historical studies in all cases. EEPRU noted that excluding studies using historic colistin breakpoints had little impact on the results for cefiderocol compared with colistin. EEPRU’s clinical advisors noted that there is very limited evidence to support the assumption that outcomes are better with colistin combination therapy than colistin monotherapy.
   * **Why it matters:** If historical breakpoints and definitions of susceptibility do not align with current understanding of the efficacy of the comparators, particularly colistin, EEPRU’s analyses may have underestimated the relative effectiveness, and therefore the incremental net health benefits (QALY gains), associated with CAZ-AVI and cefiderocol.
   * **Cross-references to committee papers for cefiderocol:** This issue is discussed in Shionogi’s consultation comments (number 6) and in EEPRU’s response to consultation comments (issue 1)
2. Is the relationship between susceptibility and outcomes likely to be constant across all antimicrobials?
   * **Context:** Although widely used in clinical practice, *in vitro* susceptibility testing it is an imperfect predictor of clinical response to treatment. There are several reasons for this, which may vary between drugs. However, the model assumes that the relationship between susceptibility data and clinical outcomes is the same for all antimicrobials.
   * **Why it matters**: The incremental benefit of the evaluated antimicrobial may be over or underestimated if there are substantial differences in the relationship between susceptibility and outcomes across comparators.
   * **Cross-references to committee papers for cefiderocol:** The relationship between susceptibility and outcomes is reviewed in the Assessment Report, Section 5.6.1. The assumptions used in the model are detailed in the Assessment Report Sections 8.2.3.3 and 8.2.3.5

# Model assumptions

1. In the empiric setting, which patients should be classed as being at high risk of having a multi-drug-resistant pathogen, and eligible for empiric treatment?
   * **Context:** EEPRU use 3 risk factors, but the company thinks the definition should be wider.
     1. EEPRU definition (one of the following): patient previously hospitalised in setting with high prevalence of pathogen of interest; or ward outbreak of pathogen of interest; or previous cultures (during current/previous hospital stay) showing infection/colonisation with pathogen of interest
     2. Pfizer definition: patients at risk of resistance due to one of the following: previous admission to ICU; longer admission times; critical illness; use of invasive devices and prior antibiotic therapy including cephalosporin, carbapenem or fluoroquinolone; symptoms or signs starting more than 5 days after hospital admission; relevant comorbidity such as severe lung disease or immunosuppression; recent use of broad-spectrum antibiotics; colonisation with multi-drug-resistant bacteria; recent contact with a health or social care setting before current admission.
     3. Shionogi consultation comments (number 50): should include any infection suspected to be multi-drug resistant (not just metallobetalactamases), all relevant infection sites (eg bone, joint and skin infections) patients who have returned from a metallobetalactamase “hot spot” abroad and should not be limited according to any particular species.
   * **Why it matters:** Patients at high-risk were included EEPRU’s model of the “high value clinical scenarios”. Including additional patients may lead to additional QALY gains in the patient-level model (however these gains may be partially offset by extrapolating to a smaller population in the population-level model). EEPRU noted that clinical advisers expressed a concern that a broader definition may lead to stewardship challenges. Committee’s guidance will need to include recommendations about appropriate use of CAZ-AVI and cefiderocol in the empiric setting.
   * **Cross-references to committee papers for cefiderocol:** EEPRU classification of risk factors is discussed in the Assessment Report, Section 4.2.4.
2. Are the PHE SGSS estimates of the proportion of patients in the empiric setting that are correctly identified as having the suspected resistant pathogen likely to be accurate, or under/over-estimated?
   * **Context (CAZ-AVI):** For CAZ-AVI the estimates of confirmed cases of OXA-48 Enterobacterales from a survey of clinicians differed from the estimates used in the base case. The base case estimate is 20% (based on SGSS data), whereas the survey estimated 57% (but only had 9 respondents which may be unreliable, therefore several scenarios were presented with different estimates). There are potential limitations in the SGSS data (see key issue 10).
   * **Why it matters (CAZ-AVI):** The results of the model are sensitive the proportion of patients correctly suspected as having OXA-48 Enterobacterales. If the proportion is lower than the base case assumption, the net health benefits of CAZ-AVI are reduced. If the proportion is higher than the base case assumption, the net health benefits increase.
   * **Context (cefiderocol):** For cefiderocol the estimates of confirmed cases of MBL Enterobacterales from a survey of clinicians differed from the estimates used in the base case. The base case estimate is 15% (based on SGSS data), whereas the survey estimated 71% (but only had 9 respondents which may be unreliable, therefore several scenarios were presented with different estimates). There are potential limitations in the SGSS data (see key issue 10).
   * **Why it matters (cefiderocol):** The results of the model are sensitive the proportion of patients correctly suspected as having MBL Enterobacterales. When this proportion is 50% or more the preferred treatment pathway is no longer to use cefiderocol empirically, but to reserve it for use in the microbiology directed setting. This results in a lower patient and population-level net health benefit, because few patients both reach the microbiology-directed setting and require cefiderocol treatment. However, the additional value of what would essentially be a stricter stewardship approach cannot be estimated by the model.
   * **Cross-references to committee papers for cefiderocol:** The approach to estimating the proportion of patients correctly identified as having the pathogen of interest is discussed in the Assessment Report, Section 8.2.3.5.

# Research recommendations

1. Are there areas of uncertainty, that are drivers of the QALY estimates, that could be substantially reduced by further data collection and research?
   * **Context:** For example, see key issues 4, 5, 10 and 17.
   * **Why it matters**: Recommendations for key areas of data collection and research may help to reduce levels of uncertainty in the evaluation of any future new antimicrobials and may also help to inform or improve data collection approaches in the UK and any other countries considering similar approaches to evaluating new antimicrobials.

# Comparators

1. Are the chosen comparators reflective of those most used in NHS clinical practice?
   * **Context:** Due to the broad range of usage for antimicrobials there are a range of potential comparator treatments.
   * **Why it matters:** The confidential hospital invoice price for cefiderocol, which is set by NHSE, will be informed by the price of the most relevant comparator treatments.
   * **Cross-references to committee papers for cefiderocol:** The comparators chosen are described in the Assessment Report, sections 4.2.4 and 8.2.1.3.

# Contract value

1. What proportion of the value gained over the model time horizon (20 years) should be assigned to the contract period (10 years)?
   * **Context:** The estimated proportion of value accrued by the antimicrobials over the first 10 years of the 20-year time horizon (41% to 65%) is lower than is typical for other drugs whose usage is stable over time (59%). To provide a suitable ‘pull’ incentive to antimicrobial manufacturers, committee may wish to assign anywhere between 60 to 100% of the 20-year value to the 10-year contract period. The decision of how much value to assign may take into account:
     1. Whether the financial reward for the company is a sufficient pull incentive
     2. Whether there is uncaptured value in the analyses
     3. Financial risk to the NHS (for example, assigning a higher proportion to the contract period increases the risk of the NHS paying more than 100% of the antimicrobial’s value over the period that it, and future generics, will be on the market, assuming they will be used after the contract period)
   * **Why it matters**: As one of the policy goals of the evaluation framework is to provide ‘pull’ incentives to developers of antimicrobials, financial rewards should at least be in line with those expected for other drugs.
   * **Cross-references to committee papers for cefiderocol:** Population incremental health benefit over the first 10 years of usage for EEPRU’s base case analyses is reported in the Assessment Report, Appendix 20, Table A20.1. Page 188 of the Assessment Report contains the unreferenced statement: “For a pharmaceutical where population size is expected to be stable over time we would expect 59% of the value to accrue in the first 10 years.” EEPRU have confirmed that this is based on data collected to inform the following publication, although the figure of 59% is not cited in the publication: Woods et al. Estimating the shares of the value of branded pharmaceuticals accruing to manufacturers and to patients served by health systems. Health Econ. 2021 Nov;30(11):2649-2666.