

Protocol for the technology evaluation of cefiderocol for treating severe aerobic Gram-negative bacterial infections

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*Please note: although we have tried to specify as much detail as possible in this document, given the complexities of defining the high value clinical scenarios, and uncertainties about the available evidence, aspects of the HVCS will be revised in the process of the project.*

# **Introduction**

Antimicrobial (AM) resistance develops when bacteria with mutations that prevent the activity of AMs are selected through selection pressure exerted by the use of AM agents. There are two major genetic processes involved: mutations in the genes native to the organism usually associated with the mechanism of action of the compound; and acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT) of plasmids / genes (e.g., transposons) (1, 2). The majority of pathogenic microorganisms appear to have the capability to develop resistance to at least some AM agents. Mechanisms of resistance include limiting uptake of a drug, modification of a drug target, inactivation of a drug and active efflux of a drug. Resistance to multiple agents can develop via successive mutations, through the dissemination of genes or through a combination of both processes.

The increased mobility of the global population has had the effect of promoting the evolution and movement of antibiotic resistance genes. For example, very high rates of extended-spectrum β-lactamase (ESBL) production among Enterobacterales strains in Asian countries has resulted in substantial use of carbapenem antibiotics, leading to the emergence of plasmid-mediated resistance to carbapenems (3). These have spread across the globe and between species. Multidrug-resistant bacteria can also spread rapidly within both hospitals and community settings, further contributing to increased AM use and heightened resistance (4), and narrowing the choices available for antibiotic treatment.

Gram-negative bacteria (GNB) pose a significant public health problem due to their increasing levels of resistance to antibiotics. This can lead to severe consequences where infections cannot be treated effectively, or where the increased risk of mortality and morbidity from infection can prevent life-saving procedures such as transplants or other invasive procedures. Enterobacterales account for many gram-negative infections in humans, including urinary tract infections (UTIs), pneumonia, diarrhoea, meningitis, and sepsis, whilst the non-fermenter gram-negative bacilli account for the largest share of infections caused by carbapenem-resistant GNB (ESPAUR, 2020).

Carbapenem resistance is a particular problem in GNB, since this constitutes the most reliable drug class for treating bacterial infections. There are two main types of carbapenem resistance, and these can be expressed in multiple pathogens:

1. **Carbapenemase-mediated carbapenem resistance** occurs when the microorganism produces an enzyme (carbapenemase) that hydrolyses carbapenem antibiotics (such as penicillins, cephalosporins, monobactams, and carbapenems) and renders them ineffective. There are multiple carbapenemase enzymes, and these are grouped based upon the similarity of their amino acid sequences according to the Ambler classification system as class A, B, C or D. Class A, C and D enzymes have a serine-based hydrolytic mechanism, while class B enzymes are metallo-beta-lactamases (MBL) that contain zinc in the active site. Each class comprises a number of variants, which include:
   * Class A: *Klebsiella pnuemoniae* carbapenemase (KPC), Guiana extended-spectrum β-lactamase (GES), Imipenemase/non-metallocarbapenemase-A (IMI/NMC), and *Serratia marcescens* enzyme (SME)
   * Class B (MBLs): New Delhi MBL (NDM), Verona integrated-encoded MBL (VIM), Imipenemase (IMP), Sao Paulo MBL (SPM), and Germany imipenemase (GIM)
   * Class C: AmpC, CMY
   * Class D: Oxacillinase (OXA)-23, OXA-24, OXA-48, OXA-58, and related enzymes

Carbapenemases are produced by a small but growing number of Enterobacterales strains, especially *Escherichia coli* and *Klebsiella pneumoniae,* and some non-fermenter organisms such as *Pseudomonas aeruginosa (P. aeruginosa)* and *Acinetobacter* *baumannii (A. baumannii)*. Bacteria producing carbapenemases may cause serious drug-resistant infections, though the profile of resistance is different for each specific variant and is influenced by the pathogen expressing the resistance, and other resistance genes the organism may have. Of the Ambler Class A carbapenemases, the KPC carbapenemases are the most prevalent, found mostly on plasmids in *Klebsiella pneumoniae.* The class D carbapenemases are frequently detected in *A. baumannii.* The class B (MBLs) have been detected primarily in *P. aeruginosa*; however, there are increasing numbers of reports worldwide of this group of β-lactamases in the Enterobacterales. The main serine-carbapenemases among carbapenemases-producing Enterobacterales (CPE) in the UK are OXA-48 and KPC. The main MBLs in the UK are NDM, VIM and IMP (5). Specifically, 12.5% of CPE are KPC, 36.5% are OXA-48-like, and 43.2% MBL (mostly NDM) in the UK (6).

1. **Non-carbapenemase carbapenem resistance** occurs through a variety of nonenzymatic mechanisms which include reduced cell membrane permeability to carbapenems through downregulation of porins (membrane proteins that allow carbapenems into the cell), or overexpression of efflux pumps which remove carbapenems from the peri-plasmic space. Such mechanisms are often considered to produce low-level resistance, and generally more treatment options are available that maintain activity against these mechanisms.

The World Health Organisation (WHO) maintains a list of priority pathogens, where, due to the development of resistance, new AMs are urgently needed. The pathogens that the WHO deems ‘critical’ priorities are: carbapenem-resistant *A. baumannii*; carbapenem-resistant *P. aeruginosa*; carbapenem-resistant, ESBL-producing Enterobacterales (where *Klebsiella pneumonia* and *Escherichia coli* account for the large majority of Enterobacterales). These pathogens are typically multidrug-resistant GNB that can cause severe infections in secondary care settings, such as pneumonia and bloodstream infections (bacteraemia), that can often be fatal (7, 8).

Early, targeted, effective and safe AM treatment is key for the management of patients infected with carbapenemase-producing carbapenem-resistant bacteria; however, reliable AM treatment options remain scarce. Therefore, individual treatment options tailored to susceptibilities of pathogens and severity of infection are the mainstay of clinical practice (5). Carbapenems are a class of β-lactams that are often reserved as a last-line treatment option for infections that are resistant to other β-lactams with a narrower spectrum of action (9). Carbapenems are considered one of the most reliable drugs for treating bacterial infections (1), therefore the emergence and spread of resistance to these antibiotics is particularly concerning, especially resistance mediated via carbapenemase which renders other treatment options ineffective. This constitutes a major public health problem due to the morbidity and mortality associated with ineffectively treated infections by these bacteria.

NICE, NHS England and NHS Improvement are currently undertaking a project to assess the feasibility of innovative models that pay for AMs based on an evaluation of their value to the NHS as opposed to the volumes used. Following the selection of two products considered to be of high public health importance, this project involves evaluation of the selected products to inform commercial discussions regarding contract value for a period of up to 10 years. The selection process was a formal procurement exercise and aimed to identify one new AM and one existing but “nearly new” AM. The products selected by this process are Cefiderocol (Fetcroja) which is manufactured by Shionogi and received its marketing authorisation in April 2020; and ceftazidime with avibactam (Zavicefta), which is manufactured by Pfizer and received its marketing authorisation in June 2016. This protocol outlines the methods for the evaluation phase of this project for cefiderocol.

Cefiderocol received a marketing authorisation in April 2020 for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options. It is an injectable siderophore cephalosporin. It has a cephalosporin backbone with a catechol moiety at the 3- position side chain. The catechol moiety chelates ferric iron, which allows cefiderocol to cross the outer membrane via the bacteria’s own active receptor-mediated iron transport system.(10, 11) The cephalosporin core then binds primarily to penicillin binding proteins, killing bacterial cells by inhibition of peptidoglycan cell wall biosynthesis.

Cefiderocol has been tested in three randomised controlled studies(12-14) (one described as a descriptive study) which recruited patients with cUTI, bacteraemia, hospital associated pneumonia (HAP), ventilator associated pneumonia (VAP), and healthcare associated pneumonia, and in two in-vitro susceptibility studies(15, 16) against carbapenem non-sensitive isolates from global sources. Cefiderocol is active against all four Ambler classes of carbapenemase in GNB, including the MBLs (class B) most prevalent in the UK (NDM VIM, IMP), and the serine carbapenemases most prevalent in the UK (KPC in class A and OXA-48 in class D)(16, 17) as well as and the non-mutational causes of carbapenem -resistance (Porin OprD, and efflux pump) in Pseudomonas. It is also active against other WHO priority pathogens on the critical list, including ESBL-producing *Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, Serratia spp., Proteus spp., Providencia spp, and Morganella spp as* well as carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.(18) With respect to metalla-beta-lactams, efficacy has been assessed in vivo in a subgroup within a small descriptive randomised study(14) who had VIM, NDM and IMP.

# **Decision making context**

The overarching purpose of the technology evaluation is to inform funding arrangements for cefiderocol in England. This drug’s funding will differ from that of drugs evaluated under NICE Technology Appraisals in two important ways. Firstly, the payment for cefiderocol will be delinked from usage volumes and, instead, represent a fixed annual payment over the term of the agreement (3 years in the first instance, followed by a potential extension to year 10). Secondly, in a NICE Technology Appraisal, the price is proposed by the manufacturer, whereas here the payment will be agreed via commercial discussions between the manufacturer (Shionogi) and NHS England, informed by the evaluation. The role of the evaluation and subsequent NICE Committee deliberations will be to provide guidance on the value of cefiderocol to the NHS in England to inform these commercial discussions. This will include providing advice on the preferred usage of cefiderocol including the role of stewardship strategies.

In previous work, EEPRU set out principles for quantitively evaluating the value of a new AM (19). The starting point for this is to identify the range of ways in which cefiderocol can be used and to compare these scenarios to the range of ways in which other comparator AMs can be used (usage scenarios). Value is defined as the expected impact of each usage scenario on population Net Health Effects (pNHEs); value is defined at the population rather than individual-patient level as payments to the manufacturer will reflect overall value. pNHEs reflect expected population-level health benefits to patients and the wider population, expected population-level costs borne by (or savings accruing to) the NHS, and a measure of the health opportunity cost of health-care funds that allows NHS costs to be converted to health foregone. As the purpose of the evaluation work is to inform a value-based payment for cefiderocol, the drug acquisition cost for cefiderocol is excluded from the calculation of pNHE. The incremental value of cefiderocol is the difference between the pNHE associated with a given cefiderocol usage scenario and the highest pNHE for clinically relevant usage scenarios that include only comparator AMs.

As the pNHEs will inform the value-based payment to the manufacturer, they should reflect the overall value resulting from expected NHS usage. Expected NHS usage, in principle, reflects both the preferred usage specified in NICE guidance and the implications of clinical decisions taken locally.

As documented in Section 1, the licensed indication for cefiderocol is fairly broad, being available to any patient with limited treatment options, regardless of the site of the infection. In practice, to control the spread of resistance to cefiderocol and preserve its long-term viability as an effective treatment option, cefiderocol may be used in a more restricted group of patients than permitted by its license. Quantifying the health and cost implications of using cefiderocol across anticipated NHS usage, even within this restricted population, remains challenging, as use is expected across infections which differ in causative organism (pathogen, susceptibility and resistance mechanism), site of the infection, health care setting and other underlying features of the health status of the patient.

The HTA will seek to characterise the value of cefiderocol across its range of expected uses using two approaches. Firstly, decision modelling will be used to assess quantitatively the value of cefiderocol in two scenarios defined by features of the pathogen, site of infection, healthcare setting and other patient characteristics, considered to represent important uses of cefiderocol (referred to as the ‘high value clinical scenarios’ (HVCSs)). Secondly, we will provide a narrative synthesis of a range of additional information to support the NICE Committee in assessing value in the overall population expected to receive cefiderocol including patients who fall outside the HVCSs.

# **Aims and objectives**

The aim of this technology evaluation is to assess the value of cefiderocol to the NHS in England for the treatment of severe aerobic Gram-negative bacterial infections when used within its licensed indications.

Specific objectives are:

1. To identify two HVCSs for which cefiderocol is expected to have a significant impact on patients’ outcomes in terms of mortality risks and health-related quality of life.
2. To establish an appropriate decision-analytic model as a framework to quantify the costs and health benefits of the use of cefiderocol under various usage scenarios compared with alternative treatments and management strategies (usage scenarios of other available AMs) in the HVCSs. To use the model to estimate costs and health effects at the individual level, but also to aggregate these to population levels (pNHEs).
3. Using systematic methods, to identify evidence to populate each decision-analytic model in (ii).
4. To use structured expert elicitation as necessary to supplement the available evidence to populate the decision-analytic models in (ii) at the levels of the individual patients and populations.
5. To use available evidence, supplemented with expert elicitation as appropriate, to indicate how the estimated pNHEs associated with cefiderocol in the HVCSs could be extrapolated to other expected uses for the product beyond the HVCSs and within the product’s licensed indications.

# **High value clinical scenarios**

## Pathogen and resistance mechanisms

An important determinant of the efficacy of existing treatment, and therefore to defining those patients most likely to benefit from cefiderocol, is the pathogen causing the infection and its mechanism of resistance.

Feedback during the NICE scoping consultation for cefiderocol, and subsequent consultation with clinical experts, has emphasised that cefiderocol should be prioritised for the treatment of patients with infections with confirmed or suspected carbapenem-resistant GNB in secondary/tertiary care. Carbapenem resistant pathogens can be categorised according to two main classes of resistance mechanisms as discussed in detail in Section 1: non-carbapenemase carbapenem resistance and carbapenemase-mediated carbapenem resistance. For infections caused by carbapenem-resistant organisms with non-carbapenemase resistance mechanisms a range of treatment options remains available. Infections caused by carbapenemase-producing pathogens have fewer treatment options. There are two main classes of carbapenemase-producers: serine-carbapenemases and MBLs. The main serine-carbapenemases among carbapenem-resistant Enterobacterales in the UK are KPC and OXA-48. The main MBLs in the UK are NDM, VIM and IMP. Cefiderocol is active against MBLs and serine-carbapenemases. It is also effective against a wide range of pathogens, including *Enterobacterales* and the non-fermenters *P. aeruginosa* and *A. baumanniI*. Based on the rates of BSI reported in the latest available data from ESPAUR,(6) the most common CR organisms are *P. aeruginosa* and *Enterobacterales.* Infections *by A.baumannii* seem to represent a lower share of CR GNB infections, but where the pathogen has OXA mechanisms of resistance (OXA-40/24, OXA-51, OXA-58, OXA-143), there are very limited treatment options. For MBLs, there are very few treatment options, and in some cases only cefiderocol is expected to be active. There may also be a use for cefiderocol in serine CPEs which have more treatment options than MBLs, for example, in a stewardship/diversity treatment strategy. We currently propose that the HVCSs focus on the treatment of infections caused by MBLs in *Enterobacterales* and *P. aeruginosa.*

## Availability of susceptibility data during the course of an infection

Infections in secondary/tertiary care are typically initially treated with empirically-chosen antibiotics. At this stage of treatment there is limited information available to inform treatment choice. Indicators of an elevated risk of carbapenem-resistance at this stage include a range of patient- and setting-specific risk factors. Patient-level factors include prior microbiology history, recent history of hospital or long-term care admissions or regular hospital-based treatments, epidemiological links to other carriers, international travel, immunosuppression and recent broad-spectrum antibiotic exposure. Setting-specific factors include being admitted to augmented care or high-risk units and local epidemiology (e.g. previous history of outbreaks) (20).

In some hospitals and tertiary care centres, screening for carriage of carbapenem resistant pathogens is carried out. Routine screening for CPE at the point of admission has recently been recommended by Public Health England for specific high-risk patients and health care settings (20). The objective of this screening is primarily to support enhanced infection control measures, surveillance and outbreak management efforts. However, information obtained via screening may also support treatment choice as colonisation with CPE is a risk factor for a CPE infection. Currently implementation of screening for CPE is variable in the UK and the level and timing of information provided via screening also varies.

At the point an invasive bacterial infection is suspected, where possible, specimens are obtained to support further diagnostic work. Various diagnostic technologies can be used to better understand the causative pathogen and how it may respond to treatment. There are broadly three layers to this:

* A **culture** is undertaken to understand the type of pathogen causing the infection.
* **Antimicrobial-susceptibility testing** is conducted to assess the *in vitro* activity of a range of antimicrobials against the pathogen in question.
* **Gene testing** may also be conducted to establish the presence of specific resistance mechanisms.

Cultures are typically available relatively quickly with antimicrobial-susceptibility testing and gene testing taking longer (typically more than 48 hours, though this depends on local availability of testing technology and laboratory capacity; e.g. centres with access to PCR testing may have information much more quickly). The availability of gene testing also varies geographically. There may be an increase in the use of gene testing in the UK in the future as PHE has recently recommended routine use of molecular or immunochromatographic assays to detect the main carbapenemase producers (21). In settings where only susceptibility data are available, this may be used alongside information on the pathogen to infer (imperfectly) the likely presence of specific resistance mechanisms.

Overall, variability in local practice, laboratory capacity and availability of diagnostic technologies means that there is likely to be significant variation in the nature and timing of the information available to inform treatment decisions.

## Overview of high value clinical scenarios

Based on feedback from stakeholders via the NICE scoping consultation and further discussion with clinical experts, EEPRU has identified two HVCSs for use of cefiderocol: microbiology-directed treatment and risk-based empiric treatment. We explain these separately here but, in practice, they are often linked in a single patient pathway.

**Microbiology-directed treatment** refers to the use of cefiderocol in individuals with infections caused by E*nterobacterales* or *P.aeruginosa* confirmed or highly suspected based on susceptibility testing to be a producer of MBLs). This group of patients has undergone susceptibility testing which may be complemented by gene testing to understand specific resistance mechanisms. As this usage of cefiderocol will require susceptibility/gene testing to have been undertaken prior to receipt of cefiderocol, this clinical scenario will focus on individuals with non-critical infections. Section 4.4 describes in more detail the Population, Intervention, Comparison, Outcomes (PICO) for this scenario.

**Risk-based empiric treatment** refers to use of cefiderocol in the empiric setting for clinically urgent patients with a high suspicion (i.e., a high risk) of carbapenem resistance but for whom information about the pathogen is very limited (susceptibility data and gene testing not yet available). Use within this HVCS should be restricted only to those patients in whom microbiology-directed treatment is likely to be considered inappropriate due to the potential delay in time to appropriate therapy. The risk-based empiric treatment HVCS is, therefore, focused on patients who meet two criteria: (i) the infection is considered clinically urgent based on a range of information including infection site and severity, and broader information relating to the health status of the patient; and (ii) the patient is considered at elevated risk of a carbapenem-resistant infection using the type of risk markers described in Section 4.2. Section 4.4 describes in more detail the Population, Intervention, Comparison, Outcomes (PICO) for this scenario.

## PICOS for high value clinical scenarios

Based on feedback from stakeholders via the NICE scoping consultation and further discussion with clinical experts, EEPRU has defined the PICOS for the microbiology-directed and risk-based empiric treatment pathways (Table 1).

**Microbiology-directed treatment:** In the microbiology-directed usage scenario, feedback from stakeholders and clinical experts indicated that cUTIs have high-prevalence and a slower clinical course than, for example, ventilator-associated pneumonia. They are also responsible for a high proportion of blood stream infections, the reduction of which is a key priority for NHSE. This site has therefore been selected for the microbiology-directed HVCS.

Clinical and stakeholder advice also indicated that cefiderocol would be reserved for infections with limited treatment options, where susceptibility is shown. This suggests cefiderocol should be reserved to treat infections caused by carbapenemase-producing pathogens. As discussed in Section 4.1, Cefiderocol is active against MBL and serine mechanisms, and against a wide range of pathogens. Based on clinical feedback, the patient group for the HVCS will be limited to patients with infections caused by MBL carbapenemase-producing *Enterobacterales* and *P.aeruginosa,* since there are extremely limited treatment options for patients with these infections, and feedback from clinicians was that they would like to preserve cefiderocol’s effectiveness by restricting its use*.*

Cefiderocol can be used as a monotherapy but may also be used in combination with other treatments, as indicated by microbiology and gene testing. In clinical practice, alternative treatment options (comparators) would be defined by the results of susceptibility and gene testing. Clinical advice indicated that for MBL mechanisms, sometime there is no alternative treatment that shows activity. Depending on susceptibility data, colistin and tigecycline as monotherapy or in combination with each other, aminoglycosides, fosfomycin, ciprofloxacin and ceftazidime-avibactam (CAZ-AVI) with aztreonam (used off-label) are potential alternative treatments. Some pathogens may be susceptible to other treatments which could be used if susceptibility testing indicates activity. High dose carbapenems may be used in some circumstances.

**Risk-based empiric treatment**: In the risk-based empiric usage scenario, feedback from stakeholders and clinicians indicated that the most frequent clinically urgent infections are HAP/VAP and blood stream infections. Given the time and resources available for this project, we anticipate we will need to focus on either the blood stream or HAP/VAP sites. This will be informed by an assessment of their relative importance and the availability of evidence to inform these scenarios. We may further refine the patient characteristics that are used to identify patients as clinically urgent, as not all infections at these sites may be considered urgent.

Patients will be those who have a high risk of an MBL mechanism (e.g. local epidemiology, previous screening results or infection, or travel history). Clinical advice currently indicates that cefiderocol may be used in combination with other broad-spectrum antibiotics in the risk-based empiric usage scenario. Other treatment options in the risk-based empiric usage scenario would be defined on a case-by-case basis and would consider information about the likely infection (e.g., colonisation or previous infection with a known pathogen/mechanism; exposure to a known pathogen; local epidemiology). Potential options include any of the treatments already listed in the microbiology-directed usage scenario used alone or in combination, as well as piperacillin-tazobactam, aztreonam, ceftolozane with tazobactam, imipenem with cilastatin and relebactam, and (high dose) meropenem used alone or in combination with vaborbactam. It was noted by one stakeholder that colistin and aminoglycosides may be less relevant in VAP. Once microbiology has confirmed the susceptibility profile and mechanisms of resistance of the pathogen, treatment may be continued or stopped, dosage may be altered, or different AMs may be initiated.

**Table 1: PICOS for the HVCSs**

| **Element** | **Microbiology-directed treatment** | **Risk-based empiric treatment** |
| --- | --- | --- |
| **Population - Patients** | Where microbiological susceptibility testing has been performed with or without gene testing | With clinically urgent disease with high risk of an infection caused by a resistant pathogen. Suspicion of infection may be based on risk factors such as screening microbiology, previous infections and treatment failures, personal contacts, travel or hospital-stay history and local epidemiology of carbapenem-resistant (CR) infections. |
| **Population - Pathogen/mechanism** | Patients with suspected or confirmed metallo-beta-lactamases (enterobacterales and *Pseudomonas spp)* of the following subtypes:   * NDM, VIM, IMP | Infections suspected to be caused by Enterobacterales or *Pseudomonas spp* which have metallo-beta-lactamase mechanisms of resistance |
| **Population - Site of infection** | Complicated urinary tract infection (cUTI) | Hospital associated pneumonia (HAP)/ ventilator associated pneumonia (VAP) and/or blood stream infections |
| **Intervention** | Cefiderocol alone or in combination | Cefiderocol alone or in combination |
| **Comparators** | Comparators used in clinical practice in England, as defined by susceptibility testing and/or gene testing and considering infection site and infiltration data. Potential comparators include:  **Metallo-beta-lactamase (MBL):**   * No alternative treatment * Colistin +/- tigecycline * Tigecyclin * aminoglycosides (gentamicin, amikacin, tobramycin) * ceftazidime-avibactam (CAZ-AVI) plus aztreonam (if carbapenem-resistant Enterobacterales (CRE) with MBL)\* * Fosfomycin * Ciprofloxacin | Comparators used in clinical practice in England, as defined by suspected infection, considering, for example, screening microbiology, previous infections and treatment failures, personal contacts, travel or hospital-stay history, local epidemiology of CR infections, infection site and penetration data, and local/national stewardship guidelines.  Potential comparators in the risk-based empiric high value clinical scenarios (HVCS), in addition to those listed for the microbiology-directed HVCS include:   * piperacillin-tazobactam * meropenem potentially at high dose * aztreonam * CAZ-AVI * ceftolozane with tazobactam * imipenem with cilastatin and relebactam * meropenem with vaborbactam   Colistin and aminoglycocides may be less relevant in VAP. |
| **Outcomes** | The outcome measures to be considered include:   * All-cause mortality * Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy is needed) * Microbiologic eradication * Emergence of resistance * Hospital days * Intensive care unit (ICU) days * Readmission rate within 90 days of treatment * Number of treatment days * Health-related quality of life * Adverse events (including those associated with Clostridium Difficile infection and renal toxicity) | As for microbiology-directed treatment |
| **Study designs** | The types of studies and data to be considered include:   * Randomised controlled trial (RCTs) * Observational studies * In-vitro susceptibility data * National, regional or international datasets * Pharmacokinetic and pharmacodynamic (PK/PD) | As for microbiology-directed treatment |

\* This is an off-label combination

# **Decision model components**

## Synthesis of existing cost-effectiveness evidence

Three types of existing cost-effectiveness evidence will be reviewed:

* Published studies of the cost-effectiveness of cefiderocol (including published journal articles and evaluations by other HTA agencies). These studies will be identified systematically. For cefiderocol a novel AM, we do not anticipate many published cost-effectiveness studies. Hence, we may consider expanding the searches to include economic evaluations of key comparators, based on discussion with the clinicians. We will also draw on the results from the ceftazidime with avibactam (CAZ-AVI) review of published cost-effectiveness models.
* Cost-effectiveness modelling submitted by the manufacturer. The manufacturer is permitted - though not required - to submit a cost-effectiveness assessment as part of the NICE process.
* Other published cost-effectiveness studies considered relevant by the study team – for example this might involve identifying evaluations of comparator technologies, evaluations in the sites of interest, or in patients with specific types of AM resistant infections. These studies will be identified via targeted reviews.

Published cost-effectiveness studies of cefiderocol (and/or key comparators) and any cost-effectiveness modelling submitted by the manufacturer will be reviewed in two levels, the first level will map their relevance to the likely use of cefiderocol in the UK and their relevance to decision making within the NHS. Following this, any studies considered pertinent to this evaluation will be appraised for quality and narratively summarised.

Studies will also be reviewed (but not necessarily subject to a formal assessment or narrative summary) to assist in the overall development of the decision-analytic model in terms of identifying important structural assumptions and potential sources of evidence/data, and by highlighting key areas of uncertainty.

## Development of a de novo economic model

A decision-analytic model will be developed to estimate the pNHE of the alternative usage scenarios for cefiderocol and comparator AMs in the HVCSs. The design of the implemented quantitative model will be preceded by a conceptual modelling phase which will be informed by the study team’s evolving understanding of the available evidence and consultation with relevant experts.

The definition of the populations within the HVCSs for which quantitative modelling is feasible will be dependent on available evidence. For example, the constellation of risk factors used to define patients as at high risk of a resistant infection within the risk-based empiric setting will depend on the availability of evidence linking specific patient characteristics to the risk of developing a resistant infection.

It may also be feasible and desirable to vary the definition of populations via sub-scenarios. For example, we may be able to explore the implications of focusing empiric treatment only on patients who develop an infection after being previously identified as a carrier of a carbapenem-resistant pathogen via screening. Again, this will depend on the nature of the available evidence.

The comparators will aim to reflect the range of treatments currently used in each HVCS as described in Section 4.4. We will explore the importance of modelling diverse prescribing strategies for cefiderocol or comparators with clinical experts. Diverse prescribing strategies can include mixing protocols, whereby a fraction of the population receives one AM and a fraction receives another, or rotation or cycling protocols where the recommended AM is varied over time. The inclusion of these usage scenarios will depend on their likely benefits as informed by clinical experts and the availability of evidence to support modelling (see Section 7 for further discussion).

The *de novo* economic model will comprise a patient-level component characterising the likely impact of cefiderocol and existing AM usage scenarios on costs, HRQoL and mortality over the lifetime of the patient; and a population-level component that aggregates the patient-level predictions to the population level accounting for the likely trajectory of infections and resistance patterns over time and potentially capturing the effects of usage scenarios on these trajectories (e.g. by reflecting effects on transmission).

Where possible the analyses will be consistent with the NICE reference case. The model perspective will be that of the NHS and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and QALYs will be discounted at a rate of 3.5% per annum. The time horizon of the patient-level component will be the lifetime of the individual patient. The time horizon for the population-level component could, in principle, be indefinite (19). The time horizon selected for the model will likely be a practical decision based on a number of considerations including discount rates and evolution of resistance to cefiderocol.

## Patient-level component

The patient-level component of the model is expected to be structured similarly to models developed as part of other NICE activities. Key aspects of model development will include estimating the short-term comparative effectiveness, and important safety implications of different usage scenarios and linking estimates of short-term comparative effectiveness to long term outcomes, particularly mortality. As discussed in detail in Section 6.1.1, for cefiderocol and other new AMs, a key challenge will be estimating comparative effectiveness as the available trial data do not focus on the patient groups defined within the HVCSs. Another key aspect of the modelling will be to link efficacy at the patient-level with the evolving profile of resistance to existing AMs and cefiderocol as modelled via the population component.

For the risk-based empiric treatment HVCS, there are likely to be a number of additional elements to the modelling. There may be a need to model treatment switching or cessation following receipt of microbiology data (including de-escalation from cefiderocol). We may also need to separate out patients according to whether they have a resistant infection or not and, possibly, according to the mechanisms of resistance of the pathogen causing the infection. This will require an estimate of the risk of resistance conditional upon patient characteristics and an assessment of comparative effectiveness in these two groups. How we approach these challenges and the granularity at which we will model various possible clinical scenarios will be dependent on the nature of the available evidence.

An important role of AMs is in ensuring that infections arising following key medical procedures can be effectively managed. The model will capture the benefits of utilising cefiderocol for treatment for cUTI, and HAP/VAP or bloodstream infections that occur following major medical procedures, but not other important procedure-associated infections such as cIAI. The modelling of enablement value is further discussed in Section ‎7.

## Population-level component

One of the most challenging aspects of the HTA is likely to be modelling at the population level. The previous EEPRU framework outlined two broad approaches to this: mechanistic dynamic transmission modelling which attempts to explain the way in which susceptible and resistant pathogens spread through the population; and statistical forecasting models that predict the number of people with infections with specific resistance profiles without explicitly modelling the underlying mechanistic processes of pathogen transmission and resistance acquisition (19).

Developing a mechanistic transmission model that characterises the spread of carbapenem-resistant organisms, with an adequate level of detail to model the introduction of cefiderocol in the HVCSs outlined above, and that is appropriately calibrated to historical epidemiological data is unlikely to be feasible within the time and resources available for this evaluation. Any mechanistic transmission models identified by our reviews or submitted by manufacturers will, however, be considered.

We anticipate that the core of the modelling will, therefore, be a forecast-based model. The implications of cefiderocol usage on the transmission of carbapenem-resistant pathogens may be explored separately if considered appropriate (see discussion below). There will be two elements to the forecasting. The first element is forecasting the growth in the eligible patient population over time for the two HVCSs: patients considered eligible for risk-based empiric treatment and patients considered eligible for microbiology-directed treatment as defined in Section 4.3-4.4. This will ideally be informed by nationally representative time-series data from the UK, with extrapolation based on statistical methods and/or forecasts elicited from experts using formal structured elicitation approaches. International data may also be used if considered relevant in understanding the likely trajectory for the UK situation.

The second element will involve predicting the rate of development of resistance to cefiderocol. We anticipate that the historical data on resistance will not be available for cefiderocol (being a new AM). Hence, we will consider different patterns of resistance over time, informed by the observed resistance profiles for older analogous AMs. This lack of historical data will also mean that extrapolation of future resistance will be associated with very large degrees of uncertainty, which we will attempt to quantify. We also foresee that there will be a need for structured expert elicitation exercises to draw out plausible future resistance trajectories. Whilst we will look for this evidence to inform resistance pattern over time for cefiderocol, we expect it to be very limited. We anticipate that resistance to cefiderocol will be functionally related to usage within the model. Modelling resistance to cefiderocol in each HVCS should account for the degree of usage of cefiderocol in the other HVCS considered. For example, high use in the empiric setting may result in higher levels of cefiderocol resistance over time and, therefore, reduced efficacy in the microbiology-directed setting in the longer-term.

During the scoping consultation and discussions with relevant experts, it became clear that there was considerable uncertainty about how the introduction of cefiderocol might impact on the likelihood of transmission of infection. A range of different pathways was postulated as to how cefiderocol could influence transmission risk and, therefore, the number of future infections arising:

* If more patients achieve clinical cure (resolution of signs and symptoms) this may reduce the risk of infection transmission. However, if transmission is predominantly driven by carriage in the large bowel, which new AMs are unlikely to affect, then this mechanism may be less relevant.
* If patients are treated successfully, they may experience a reduced time in hospital thus reducing the risk of onwards transmission.
* If patients are treated successfully, this may only reduce their mortality risk but increase their time in hospital and thus increase the risk of onward transmission.

Further discussion with relevant experts is required to establish whether cefiderocol is expected to have an important impact on disease transmission, and therefore whether this represents an important area for further modelling. If this is identified as an important area for modelling, we will explore alternative approaches to capturing the effect of cefiderocol on transmission including a simple transmission model or scenarios describing impacts on infection rates. Further details on the approach to reflecting transmission value are provided in Section ‎7.

## Outputs of economic analysis

Estimates of expected NHEs will be presented at the patient and population level and aggregated across the HVCSs. Standard methods will be employed to explore the sensitivity of the pNHE estimates to the underlying structural assumptions of the model, parameter inputs, discount rates and time horizon. This will include reflection of uncertainty around the likely rate of emergence of carbapenem-resistant infections over time and, therefore, to capture the possibility of spikes in the prevalence of resistant infection. Distributions of incremental pNHEs will be presented to the committee to support their understanding of the potential for cefiderocol to avoid low probability but major “catastrophic” health consequences. This has been identified as a potential additional element of insurance value in the literature around the economic evaluation of new AMs (19, 22).

# **Evidence requirements**

## Evidence in the evaluation of new antimicrobials

In comparison to a standard HTA, the data available for evaluating new AMs are less straightforward. This is largely because the randomised controlled trial (RCT) evidence is primarily generated for regulatory purposes, to demonstrate safety and efficacy against a range of pathogens. Trials are usually non-inferiority in design (usually with a -10% margin), which poses challenges when conducting evaluations of comparative efficacy with other treatments, and difficulties with parameterisation in cost-effectiveness modelling since superiority is not usually demonstrated in these trial designs. Comparators tend to be best available therapy, which may not match clinical practice in England since best practice is highly variable due to local protocols reflecting testing capacities and the microbiological epidemiology in a given area. Extensively drug resistant patients, such as those with MBL infections, are usually excluded since it would be unethical to randomise patients to an ineffective comparator treatment. In addition, testing for the resistance mechanism and subsequently enrolling patients may introduce critical delays in their treatment. Such regulatory trials also do not tend to address differences in treatment pathways, such as the microbiology-directed and risk-based empiric usage scenarios, or differences in stewardship protocols, such as rotation of AMs, mixing treatments, or combination therapies.

As such, these studies have limited value to the evaluation of new AMs in a HTA context, and there is a greater need to consider a broader set of evidence. Evidence to inform the cost-effectiveness modelling will be drawn from a number of different sources. We have categorised these into three broad types:

1. Clinical evidence to inform patient-level components
2. Clinical evidence to inform population-level components
3. Non-clinical evidence: costs and utilities

In all cases, evidence will be selected according to a balance of relevance and study quality, as recommended in the Decision Support Unit Technical Support Document 13 (see Section 6.2) (23).

## Evidence to inform patient-level components

Patient-level components are those that link patients and their characteristics to surrogate or clinical outcomes. Evidence may be specific to a given pathogen, mechanism or site or a combination of these features.

**Effectiveness**

Data relating to the effectiveness of cefiderocol and its comparators will be identified from several sources. RCT evidence and subgroup data from RCTs will be used where possible and of relevance to the decision problem specified in the HVCSs. For example, safety data is likely to be generalisable across pathogen/mechanism/site combinations, and some in vitro data is available for the mechanism of interest to the HVCS (see Section 1) from at least one RCT. Where evidence from RCTs is not generalisable to the HVCSs, or generalisability is unclear, other sources will be consulted. This is likely to be the case for key clinical outcomes relating to the efficacy of the treatment, since the trial populations recruited unknown or relatively small numbers of patients with the characteristics defined by the HVCSs. Prospective or retrospective observational studies, or data from registries, where specific pathogens/mechanisms are treated with cefiderocol or comparators and patients are followed over time, may provide evidence of short- and long-term clinical outcomes. If RCT and observational *in-vivo* evidence is sparse, contradictory, inconclusive or if *in-vitro* data may add value to the estimation of absolute and comparative efficacy, *in-vitro* susceptibility testing data and evidence relating susceptibility testing to clinical outcomes from published studies or grey literature sources may be consulted. Efficacy data relating to escalation or de-escalation of treatment in response to susceptibility testing and relating to diverse prescribing strategy will also be sought in the same manner if these are deemed to be important features of the treatment pathway. There may also be a role for pharmacokinetic/pharmacodynamic data depending on the availability of other evidence.

**Risk level**

In order to identify the proportion of patients within a treated population in the risk-based empiric usage scenario who are then confirmed to have the target pathogen/mechanism, it will be necessary to quantify the risk of infection due to a given pathogen/mechanism according to patient characteristics. There are a number of sources where such data could be reported, including observational studies, risk stratification models (e.g. the Imperial model (24)) or grey literature datasets (national, local or international).

**Prognosis**

RCT and observational data may not provide long term outcomes for patients according to their status after treatment (cured, not cured) and their key baseline characteristics. Long term outcomes may vary by pathogen, mechanism, site of infection or other patient characteristics such as comorbidities, time to treatment, and severity of infection. Long term outcomes will likely be of key importance to the model. Data sources that will be consulted include trial data, observational studies and routine datasets (national, local or international) that report relevant data linking short term outcomes to long term outcomes.

## Evidence to inform population-level component

When estimating pNHEs it is important to extrapolate from the modelled patient sample to the broader eligible population. This will require estimates of the eligible population, and how it is likely to vary over time. There may be no unique way to define the eligible population, but it is anticipated to be influenced by patient risk characteristics for the severity of infection (in the risk-based empiric HVCS) and the number of patients with specific microbiology features such as the presence of MBL carbapenemases (for the microbiology-directed HVCS). Changes in the eligible population over time will be influenced by changes in the level of resistance, which in turn will be influenced by levels of use for both the AM of interest and alternative AMs.

It is anticipated that the majority of evidence required to estimate resistance profiles, and hence the population-level component, will be obtained from the grey literature. This includes routine surveillance data such as the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) (6) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) (25). Where possible, preference will be given to English data, resulting in the following hierarchy of evidence sources:

* National UK datasets.
* UK local or regional datasets (such as those from hospitals or trusts)
* UK-based observational studies
* International datasets that are judged to be relevant to the UK setting
* Non-UK-observational studies that are judged to be relevant to the UK setting.

These data sources will provide evidence to inform modelling assumptions and inputs relating to how the eligible patient population varies over time and how resistance evolves over time (which may also require evidence on how prescribing of AMs has evolved over time). Where additional modelling is undertaken to characterise the impact of cefiderocol on transmission, targeted searches will be developed to inform the evidence requirements for this modelling, such as rates of transmission.

It is anticipated that relevant datasets and studies will be identified via discussion with clinical experts, complemented by targeted literature searches. Where there are outstanding evidence gaps, expert elicitation will be considered. Statistical methods, such as time series models, may be employed to generate forecasts of future population and resistance values, and expert elicitation will be considered as an option to validate or to inform these extrapolations. Whilst every effort will be made to quantify the eligible population (including its variation over the time horizon of the analysis) as accurately as possible, this will be ultimately driven by the granularity and relevance of the identified evidence.

## Non-clinical evidence: costs and utilities

Baseline utility data will primarily be obtained from standard sources (26). The feasibility of updating these using more recent UK datasets (such as Health Survey for England) will be explored. Where possible, baseline utility data will reflect the baseline characteristics of the population. This includes age, gender, and the presence of co-morbidities. Changes in baseline utility over time due to ageing will be included. Evidence on the impact of infections and adverse events will also be captured. The values for these will be obtained from a targeted search of health-related quality of life studies (using systematic methods), complemented by existing economic evaluations (as identified via the review of cost-effectiveness evidence described in ‘Decision model components’). If multiple evidence sources are available, preference will be given to studies reporting directly estimated EQ-5D values (either three-level or five-level), followed by studies that report mapped EQ-5D values. Where evidence gaps remain, assumptions will be made and checked with clinical experts. The identification and incorporation of evidence on utilities will, as far as possible, follow good practice (27).

A number of costs will be obtained from routine national sources. This includes the costs of comparator AMs (British National Formulary and electronic market information tool), hospital stays and hospital procedures (the UK Personal Social Services Research Unit Costs of Health and Social Care, NHS reference costs). The acquisition cost of cefiderocol will not be included in the economic evaluation. Other cost inputs (such as the costs of treating adverse events) as well as any required estimates of resource use, will be obtained from the literature (including existing economic evaluations or, if required, targeted literature searches) or via clinical input. All costs will be inflated to current-day prices using PSSRU inflation indices, with conversion to UK £ using purchasing power parities where necessary.

## Methods for identifying and reviewing evidence and the role of elicitation

The retrieval of evidence will be an iterative process, driven by the emerging requirements of the model, and the identification of high-quality data with high relevance to the HVCSs. The methodology is summarised in Figure 1. Traditional systematic reviews of clinical efficacy data have a deep and narrow focus. Since the evidence requirements for new AMs in this health technology context are more complex and wide ranging, the focus is necessarily much broader, and review methods have been adapted accordingly. The methods applied will be systematic and transparent, and will follow the principles outlined in the Decision Support Unit’s Technical Support Document 13 (23) which outlines how to identify evidence for cost-effectiveness modelling.

**Evidence mapping**

In the first instance, an evidence map of the requirements listed in Sections 6.1.1-6.1.3 will be constructed. We anticipate that the map will be based on evidence submitted by experts and stakeholders and will be supplemented by focused searches of key bibliographic databases (see “Search strategy” below). If the searches are necessarily large, a pragmatic approach to sifting may be taken, using techniques such as sorting references by date order, and “dredging” the database using keywords, key authors and key journals. The map will aim to identify key and important sources of data, but not be exhaustive.

To aid *evidence selection and review*, the map will tabulate key study characteristics (e.g., study design, sample size, population, pathogen, mechanism, site, outcomes reported), but will not include data relating to study quality or numeric outcomes. It will draw on all potential sources of evidence, including systematic reviews, RCTs, observational studies and national, local or international datasets identified in the grey literature.

The mapping process will also identify initial data relevant to Section 8.

**Evidence selection and review**

From this map, data sources will be assessed in turn for relevance to the model, starting with studies with the clearest relevance to the HVCSs and continuing until appropriate high quality, relevant sources are identified. Where preferred sources (as detailed in Sections 6.1.1-6.1.3) do not yield data, additional focused searches may be employed to ensure studies have not been missed (see “search strategy” below). Where additional searches still do not yield data, lower levels of evidence may be considered, or elicitation may be performed to fulfil the evidence requirement (see Section “Elicitation of evidence” below).

**Presentation of data**

Data sources drawn from the evidence map and considered for inclusion will be tabulated and reasons for their exclusion provided. Data not selected for inclusion in the model will not be assessed further. Data sources selected for inclusion in the HVCSs will be data extracted, quality assessed (key model inputs only), tabulated, and statistically synthesised (where appropriate, see Section 6.3). These studies will be presented in a narrative summary that describes the process of selection and gives a clear rationale for the selection of data that enters the model.

**Elicitation of evidence**

The evidence used to establish the value of cefiderocol is likely to be uncertain. For example, the evidence base may be: 1) insufficiently mature, e.g., insufficient sample sizes or limited follow-up time (temporal uncertainty); 2) biased, e.g., limitations in the design of the research study or not relevant to the patient population under study; or 3) entirely missing. There are likely to be uncertainties for both the patient-level components and the population-level components of the model. Where no evidence of high quality and relevance to the decision problem is identified, elicitation may be required.

With a less developed evidence-base, judgments based on consultation with individuals, who have expertise on the subject matter, can be used (termed expert elicitation). Elicitation will be used here to supplement experimental and non-experimental evidence and to populate and validate the model. A structured elicitation process will be used to improve accountability and transparency. Specifically, the reference methods developed at York as part of the MRC elicitation work (28) will be employed. These reference methods retain a degree of flexibility, in particular on the convening of experts either through consensus or through individual elicitation, a consideration that may be relevant given the likely lack of observed clinical experience for some of the parameters of interest. Which experts to consult will be determined in collaboration with NICE and clinical experts. The elicitation will be designed and conducted according to an elicitation protocol, which will be specified once the models’ requirements have been determined.

**Search strategy**

Searches to inform the evidence requirements I, II and III will be characterised by the following:

* Conventional search to identify studies of specific study designs. The InterTASC Information Specialists’ Sub-Group (ISSG) filter resource (29) can inform these high-precision searches
* Multiple and brief exploratory searches of the internet for grey literature e.g., including national, local and international data sets
* Expert-recommended resources such as specialist databases and sources of information such as routine data, registries and administrative data.

To maximise the rate of return of potentially relevant information, the search will be systematic but will focus on precision rather than sensitivity and may adopt various search techniques and approaches as recommended in DSU TSD 13:(23).

* One-line filter searching using high precision filters such as McMaster Hedges search filters.
* Restricting the number of sources searched and/or focusing on specialist databases such as CENTRAL and NHS EED.
* Restricting search terms to within specific fields such as title only searching.
* Identifying high yield patches - where one source of information is able to meet multiple information needs within the model.
* Proximal cue or information scent searching could be used as a starting point and this includes ‘snowballing’ technique of forward and backward citation searching.
* Information gathering using secondary or indirect retrieval to inform the directed retrieval process.

There will be a systematic literature search of published literature to identify cost-effectiveness models relevant to the decision problem. Electronic databases will be searched including MEDLINE (via Ovid), Embase (via Ovid) and the Centre for Reviews and Dissemination databases (University of York). Supplementary searches will include previous HTAs and conference proceedings not captured in the database searches.

## Statistical analysis and synthesis of evidence

For clinical efficacy endpoints for which there is interest in simultaneously comparing all treatments options, network meta-analysis (NMA) will be considered. An NMA is an extension of a standard pairwise meta-analysis that coherently summarises all direct and indirect evidence about treatment effects and allows a simultaneous comparison to be made between all pairs of treatments (30).

It is anticipated that is there is unlikely to be a connected network of evidence and so incorporation of single arm RCTs and non-randomised studies to infer comparative efficacy will also be considered. Naïve unanchored indirect comparison (where individual arms of different studies are naively  
compared with each other) are likely to provide biased estimates of relative efficacy due to lack of randomisation. Where individual patient data (IPD) are available for at least one study of interest, population adjustment methods will be considered (31, 32). Where empirical information is not available, elicitation methods will be considered to inform the bias arising from the use of observational evidence (33). Analyses will be conducted in the freely available software package R (34) using a suitable MCMC sampler such as WinBUGS (35). Alternatively, dependent on time and resource constraints, the analysis may be restricted to aggregate study level data only.

**Figure 1: Flow diagram of the evidence review process**

**Searches**

Focussed, pragmatic searches of key sources (expert/stakeholder suggestions, grey literature, bibliographic databases)

**Evidence map**

Tabulation of potentially relevant data sources identified by searches

Tiered approach to **assessment** of data sources against model requirements, starting with highest quality and/or relevance

Identification of data sources with relevance to full value to NHS

**Selection** of highest quality data with highest relevance to the model

Additional focussed pragmatic searches

**Synthesis**

Formal data extraction and synthesis where appropriate

**Elicitation**

Elicitation of model parameters where no data available, or helpful to aid parameter choice

**Used in Model**

# **Incorporating all elements of the value of** cefiderocol

The literature on the economic evaluation of AMs has described the different sources of value associated with these products (19, 22). In EEPRU’s earlier work on evaluation methods (19), the principles by which each of these ‘elements of value’ can be reflected in models focused on estimating the impact of new products on net population health benefit was discussed. The challenge is the availability of evidence and the scale of the modelling necessary to do this. Table 2 below sets out how the evaluation for cefiderocol will consider these elements of value given suitable evidence as well as sufficient time and resources. It also shows how we will approach this using more descriptive approaches if quantification proves unfeasible. A key stage of this work will be for clinical advisors to provide guidance on which elements of value are considered to have the greatest potential to impact on population health outcomes and, as such, should be considered the highest priority for quantitative modelling of the HVCSs.

**Table 2. Potential elements of value relating to the use of cefiderocol**

| **Element of value** | **What this represents** | **Modelling approach and necessary evidence** | **Possible approaches if modelling not feasible** |
| --- | --- | --- | --- |
| Enablement value | Impact on population health from additional medical procedures being possible as a result of cefiderocol being available to manage otherwise resistant infections with few alternative treatment options. | Having received a procedure could be one of several characteristics (or risk factors) associated with the high value clinical scenarios (HVCSs). Within HVCSs we may be able to estimate an upper bound on enablement value by looking at the net health outcomes in patients who develop a post-procedural infection and are treated with and without cefiderocol. | Approaches to dealing with the value associated with other clinical usage scenarios, including usage in post-procedural infections not within our HVCSs are considered in Section 8. |
| Diversity value | Impact on population health over time as a result of cefiderocol being available and adding to the range of treatments currently available. This can result in a reduction in selection pressure on and resistance to other available treatments, hence retaining their effectiveness for longer. | In principle, modelling can capture diversity value for the HVCSs by comparing alternative decision options which, as well as cefiderocol, include rotation of AMs and mixing protocols where a fraction of the population receives different AMs.  As well as evidence on the efficacy of these options, this would also need evidence on the impact on pathogen resistance over time to the novel and existing antimicrobials. | In the absence of the formal evidence needed for the HVCSs, we will consider using expert elicitation to quantify resistance changes over time under different stewardship strategies.  Approaches to dealing with the value associated with other clinical usage scenarios for cefiderocol within its license is considered in Section 8. |
| Insurance value | Insurance value is presented in the literature in different ways (19). One relates to the impact on population health over time as a result of cefiderocol being ‘held back’ in reserve until resistance to existing treatments effectively eliminates the latter as options. Resistance to cefiderocol would be limited due to being used less.  A second meaning is that cefiderocol would ameliorate a potentially catastrophic situation where multi-drug resistance becomes so widespread that cefiderocol is the only option across a large number of clinical scenarios. This is a low probability but high consequence outcome. | Capturing the first meaning has similar evidence implications to diversity value. Holding cefiderocol in reserve is a decision option which can, in principle, be evaluated alongside stated comparators as part of stewardships arrangements.  Capturing the second scenario could, in principle, be part of quantifying the positive incremental pNHEs of cefiderocol as a distribution of probabilistic states of the world, one of which could be the type of catastrophic situation of relevance here. Low probability high consequence events in the ‘tail’ of this distribution can be highlighted, although these should be considered in the context of the full distribution. | The first meaning could be handled as for diversity value. |
| Transmission value | The impact on population health over time as a result of cefiderocol reducing the rate of transmission of a given pathogen from patients treated with that product to other individuals, potentially reducing the rate of resistant infections requiring treatment. | In principle, transmission modelling could be used to reflect these impacts. It would require an understanding regarding how cefiderocol would reduce transmission and evidence for the magnitude of this effect. For example, if evidence indicates that cefiderocol reduces patients’ average length of stay in hospital, and duration of hospital stay impacts on transmission rates, this could provide a means of estimating transmission value. | Clinical opinion will guide us regarding any mechanism(s) by which cefiderocol may affect transmission as part of the HVCSs. Evidence relating to such mechanism(s) will be sought. Depending on the type, quality and extent of this evidence, modelling may be possible. Otherwise, any available evidence will be presented independently of the modelling.  Approaches to dealing with the value associated with other clinical usage scenarios for cefiderocol within its license is considered in Section 8. |
| Spectrum value | Benefits of cefiderocol replacing broad spectrum AMs and the problems associated with their over-use: potential collateral damage to the human microbiome resulting in a greater chance of developing resistance to the AMs used. | To reflect this explicitly in the modelling would be extremely difficult, needing evidence on (i) the extent to which having cefiderocol available would reduce the use of broad-spectrum AMs; (ii) how this reduction would feed through to change in resistance; and (iii) how that change in resistance would impact health outcomes at individual level. Such evidence has a low likelihood of existing. | This may be reflected in our attempts to look at how changes in resistance over time (for comparators and cefiderocol) affects population health effects of cefiderocol, but that won’t be through the specific mechanism of it reducing the use of broad-spectrum antibiotics. |

# **Assessing the value of cefiderocol beyond the high value clinical scenarios**

Given the available time and resources for this evaluation, the focus of the modelling and associated evidence review will be on the HVCSs. However, NHS payment decisions will be based on the estimated total value of cefiderocol based on its expected use within the product’s license. To help to bridge this gap, it will be necessary to bring together any available evidence to quantify or describe the potential wider pNHEs of the product outside of the HVCSs. A range of approaches will be considered for this based on available evidence, including:

* Relevant evidence submitted to the process by the manufacturers of those products being evaluated.
* Use of relevant documentation and expert clinical opinion to define the other clinical scenarios in which cefiderocol might be considered consistent with its license.
* Contextualising the numbers of patients expected to benefit from cefiderocol in the HVCSs alongside those numbers of cases associated with other clinical scenarios within the product’s license.
* Using clinical opinion to estimate the magnitude of health benefit associated with the use of the products in wider clinical scenarios consistent with the product’s license.
* Identifying any relevant published economic evaluations which present suitable economic evaluations of cefiderocol in these wider clinical scenarios. Such studies would be identified in the systematic review referred to in Section 5.1 and in manufacturers’ submissions.

We anticipate that this will be narratively synthesised for presentation to the committee. However, quantitative modelling to extrapolate from the HVCSs to the broader population in which cefiderocol is expected to be used may also be explored, given time and resources permitting.

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