**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Cefiderocol for treating severe aerobic Gram-negative bacterial infections

# Response to consultee and commentator comments on the draft remit and draft scope

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Section: Background information

| Consultee/ Commentator | Comments [sic] | Action |
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| Shionogi | PHE/NICE guidance (‘Start Smart, then Focus’) is highlighted. We endorse the principles of this guidance, and it supports the patient populations that are suitable for treatment with cefiderocol (i.e. ‘suspected’ use, and then/ or ‘confirmed’ use) as described in more detail below. It will be important to carefully consider what the practical application of this principle means in a range of specific clinical scenarios (as highlighted by some of the Scope questions), and in relation to the EEPRU additional value elements. Clinical guidelines are a useful source of information on likely NHS management patterns. However, ‘real world’ evidence on actual management practices may differ and is also (arguably even more) relevant. For example:* The time taken to obtain test results from cultures and undertake clinical review in typical NHS practice may differ from that (i.e. 48-72 hours) as described in ‘Start Smart, Then Focus’.
* Guidance on use of antimicrobials (e.g. Hawkey 2018; Hughes 2020) may not fully describe or explain the agents/regimen used across the range of various specific clinical situations.

Manufacturers may be aware of – or have access to – such ‘real world’ data, that NICE/EEPRU could use for this assessment.  | Comment noted. No action required. |
| Shionogi | There is no information specifically on epidemiology in the Background, or elsewhere in the draft Scope. It is concerning that this is not more prominent, as it is necessary for the intended Population Health Benefit analysis and assessment of additional value elements that have been proposed by EEPRU and NICE. What types of population-level information do NICE anticipate a requirement for, what sources will be used to obtain data, and what further analysis or expert opinion will be obtained to generate suitable estimates? It would be helpful to understand how NICE/EEPRU plan to address these questions.  | Comment noted. The background section is only intended to provide a brief description of the infections, pathogens and current management options. No action required. |
| Shionogi | The ongoing collection of in vitro surveillance data on a broad range of antimicrobials and pathogens is also important; companies can support in providing that information. | Comment noted. No action required |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | * Microorganisms don’t “adapt and become immune” to antimicrobials – rather, bacteria with mutations that prevent the activity of antimicrobials are selected for through evolutionary pressure.
* Resistance can spread through transfer of resistance genes between bacteria and also by the transfer of resistant bacteria. The transfer of resistance genes is very important when considering carbapenemase resistance.
* Infection prevention interventions including identification of patients carrying resistant bacteria, isolation, hand hygiene, environmental cleaning, are as important as antimicrobial stewardship in controlling the emergence of resistance.
* Carbapenem resistance needs further specification. The two major causes are the combination of low-level resistance mechanisms (reduced permeability, ESBL, AmpC, and drug efflux) and carbapenemase production. Within the latter, the two main types of carbapenemase enzymes are those with zinc at the active site (metallo-carbapenemases including NDM, VIM and IMP) and those with serine at the active site (KPC and OXA-48). These distinctions are important because: 1. there are a number of alternative treatment options for non-carbapenemase carbapenem-resistant bacteria, 2. Cefiderocol is the only antibiotic with activity against metallo-carbapenemases (it is also active against serine carbapenemases).
* Gram negative bacteria (Enterobacterales such as *E coli* and *Klebsiella pneumoniae*, and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) cause a wide range of infections. Urinary tract sources account for the majority of *E coli* infections, including bloodstream infections. Other frequent infection sites include intra-abdominal and hepato-biliary infection. Other than in intensive care, these bacteria are an unusual cause of pneumonia.
* “Start smart, then focus” applies specifically to the management of patients with “red-flag” sepsis. In all other cases, empirical antibiotic treatment should aim to be as narrow spectrum as possible, based on the most frequent causative organisms and the usual antibiotic susceptibilities.
* The large majority of infections in secondary/tertiary are treated throughout the infection by empirically-chosen antibiotics without reference to positive cultures. This is because either relevant microbiological specimens are not collected prior to antibiotic initiation, cultures do not identify the bacterial cause in time to make a difference, or there is clinical indifference to the result.
 | Comment noted. Please see response to comment on background by Shionogi. No action required. |
| NHS England & NHS Improvement | The background section describes what AMR is, the WHO priority pathogens and the principles of antimicrobial stewardship but doesn’t describe the background to this initiative: i.e. the reasons why a new payment model is required.  | Comment noted. Please see response to comment on background by Shionogi. No action required. |
| NHS England & NHS Improvement | Minor factual inaccuracy in the final paragraph of this section: prescribing decision 3 in Start Smart, Then Focus is to change antimicrobial (not necessarily IV). | Thank you for your comment. The background section has been updated accordingly. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Would be helpful to add that Cefiderocol will mainly be as directed therapy for resistant infections due to the specified organisms based on laboratory results. Therefore reference to the ‘Start Smart, Then Focus’ algorithm is less relevant as it primarily applies to empirical therapy. Perhaps better to include something about review and de-escalation if appropriate. | Comment noted. Please see response to comment on background by Shionogi. No action required. |
| MSD  | No comment | Comment noted. No action required. |
| Public Health Wales  | No comment  | Comment noted. No action required. |
| Pfizer Ltd  | No comment | Comment noted. No action required. |

## Section: The technology / intervention

| Consultee/ Commentator | **Comments [sic]** | **Action** |
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| Shionogi | The list of pathogens that cefiderocol might be efficacious against could be expanded and simplified to refer to the entire Enterobacterales family instead of individual pathogens. For example, cefiderocol is likely to be effective against Shigella (ref: Ito 2018) even though this particular species is not listed in the SmPC. It is also critical to describe antimicrobial technologies’ activity profiles at a more granular level, i.e. according to specific resistance mechanisms, not just pathogen species. For example, cefiderocol is highly active in the presence of metallo-betalactamase (MBL) and porin/efflux resistance mechanisms, against which very few alternative antimicrobials are active (ref: Thalhammer 2018; Tamma 2018), and which may contribute to make certain infections multidrug resistant (MDR), extensively drug resistant (XDR) or pan drug resistant (PDR). As highlighted in the EEPRU report and in NICE’s HTA process guide for this project, the in vitro susceptibility evidence base is the primary source of such data (Yamano 2019; Longshaw 2020).  | Comment noted. The technology section is only intended to provide a brief overview of the technology. No action required. |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comment  | Comment noted. No action required. |
| NHS England & NHS Improvement | It is pertinent to include mention of information from Section 4.4 of the Marketing Authorisation for cefiderocol that states: “A higher all-cause mortality rate was observed in patients treated with cefiderocol as compared to best available therapy (BAT) in a randomised, open-label trial in critically-ill patients with infections known or suspected to be due to carbapenem-resistant Gram-negative bacteria. The higher day 28 all-cause mortality rate with cefiderocol occurred in patients treated for nosocomial pneumonia, bacteraemia and/or sepsis [25/101 (24.8%) vs. 9/49 (18.4%) with BAT; treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with cefiderocol through end-of-study [34/101 (33.7%) vs. 9/49 (18.4%) with BAT; treatment difference 15.3%, 95% CI (-0.2, 28.6)]. The cause of the increase in mortality has not been established. In the cefiderocol group there was an association between mortality and infection with *Acinetobacter spp*., which accounted for the majority of infections due to non-fermenters. In contrast, mortality was not higher in cefiderocol vs. BAT patients with infections due to other non-fermenters.” | Comment noted. All relevant evidence will be considered by the evaluation committee. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | It would be helpful given the discussion at the scoping workshop to note participants suggested potential use in other resistant infections e.g. CF, bronchiectasis. | Comment noted. All relevant evidence will be considered by the evaluation committee. No action required. |
| MSD  | No comment | Comment noted. No action required. |
| Public Health Wales  | No comment  | Comment noted. No action required. |
| Pfizer Ltd  | No comment | Comment noted. No action required. |

## Section: Population

| Consultee/ Commentator | **Comments [sic]** | Action |
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| Shionogi | Broadly, yes.However, it is important to understand what ‘limited treatment options’ means, and how this consequently means there are two separate categories of patient population – i.e:1. where a pathogen and/or resistance is identified in the ‘**confirmed**’ setting
2. a critically ill patient where an urgent intervention is required in the ‘**suspected**’ setting

Both patient types are potentially suitable for treatment with cefiderocol. These two populations represent distinct clinical settings, with different comparators and outcomes of relevance. Shionogi recommend that two ‘primary indications’ should therefore be identified for detailed analysis, one within each of these categories, and it may therefore be helpful for NICE to develop a PICO-based Scope for each, separately. As discussed at the workshop/s, it is also important to understand how the selection of patients for cefiderocol will be predominantly ‘germ based’, with other factors – such as severity of infection, patient health status, and infection site – also being considered. This synopsis is explained in more detail below. Cefiderocol has a ‘pathogen-based’ indication for treating Gram-negative infections, when there are ‘limited treatment options’. One key implication of this is that there are no infection sites in which the use of cefiderocol should be excluded from a regulatory perspective. The second key consideration is what ‘limited treatment options’ means in practice. As discussed at the workshop, this should be interpreted to mean either:1. The particular causative pathogen species and/or resistance mechanism has been identified following analysis of antibiotic susceptibility testing – i.e. making the clinical setting **‘confirmed’ carbapenem resistant** – and when these antibiogram results indicate that few antimicrobial treatment options exist that are effective against that specific pathogen.If/when the more precise nature of that resistance (e.g. resistance mechanism) is diagnosed, then treatment options are further limited to those expected to be effective against that particular mechanism. Since this testing can typically take 3-4 days, waiting for this type of confirmation before initiating antibiotic therapy tailored for carbapenem resistance is more suitable for patients that have a slower progressing infection such as cUTI. In some cases, confirmed use may effectively be a continuation of suspected use, i.e. when testing confirms the previous suspicion and when the previously selected antibiotic therapy remains appropriate.

or1. In a scenario where the patient’s health status is critical with clear signs of infection, that requires immediate antibiotic treatment initiation, and the causative pathogen or resistance mechanism is not yet known, time to effective therapy must be limited to as immediate as possible. When, in addition, there are clear risk-factors for carbapenem resistance – i.e. making the clinical setting ‘suspected’, there are limited treatment options with a high probability of covering against the full range of carbapenem resistant pathogens and resistance mechanisms. This makes the clinical setting **urgent and ‘suspected’ carbapenem resistant** - where immediate effective therapy is imperative for patient survival.

Critical can be described as being at high risk of clinical deterioration, due to the nature of the infection and/or the patient’s underlying health status, e.g. they have BSI (Blood Stream Infections), sepsis/septic shock (regardless of origin of infection), VAP (Ventilator Associated Pneumonia) or severe HAP (Hospital Acquired Pneumonia). These patients will often be in ICU, with ventilation, possibly immunosuppressed, etc.CR risk factors include having received a positive screen for a CR-GN (carbapenem-resistant Gram-negative) pathogen, having been an inpatient in a high-risk hospital abroad in the past 12 months in a high prevalence CR area, having been an inpatient in a hospital ward with known CR outbreak, previous failure on carbapenem therapy, etc.In this situation, clinicians may consider there to be limited treatment options that would sufficiently reduce the risk of treatment failure (and therefore likely death) for these critically ill patients, i.e. treatments with a satisfactory probability of being effective against the range of potentially causative pathogen species and/or resistance mechanisms. Selecting therapy that is subsequently found to have been ineffective (i.e. in hindsight, once test results have been obtained) in patients who are deteriorating rapidly, cannot be risked, and means that only a few antimicrobial therapies (i.e. those with a high likelihood of being active against an as yet unidentified pathogen) are suitable. Treatment in this setting may also be referred to as ‘directed empiric’ therapy or ‘targeted early’ therapy. As outlined above, the in vitro susceptibility data describes the activity profiles of antimicrobials against the range of pathogen species and/or resistance mechanisms. This is based on surveillance studies where for each pathogen the minimum inhibitory concentration (MIC) is determined establishing the activity of the different medicines for each isolate/pathogen. This data is often presented in the form of ‘traffic light’ charts, illustrating the relative likely effectiveness - e.g. from ‘red’ (inactive) through ‘amber’ (intermediate) to ‘green’ (likely to be active) – of alternative treatment options. (e.g. ref: Thalhammer 2018; Tamma 2018). Accordingly, this data can identify pathogens for which there are limited treatment options (i.e. few antimicrobials with ‘green’ activity status). A further consideration is antimicrobial toxicity. This is particularly relevant for polymyxin-based therapy; whilst colistin-based regimens may have quite broad activity, their benefit and suitability – particularly as options in the ‘suspected setting – is limited by significant renal adverse events.Currently, there is a particular lack of treatment options for these pathogen types:* MBL producing Enterobacterales and *Pseudomonas spp*
* XDR *Pseudomonas spp*
* CR *Acinetobacter spp* and intrinsically CR *Stenotrophomonas spp*

Cefiderocol is active against all these Gram-negative pathogens and UK-relevant associated resistance mechanisms and is therefore a suitable treatment for patients when any of the ‘target’ pathogen types listed above have been either confirmed or are suspected (and when the patient is also considered ‘critical’).Based on these principles of eligibility and criteria that can be used to identify areas of highest unmet need (see comments in Economic analysis section below), Shionogi propose the following two ‘primary indications’ for the detailed NHB analysis. These represent patient populations of high value and significant frequency.1. **‘Confirmed CR, with MBL presence’ indication**

Initiation of cefiderocol therapy when carbapenem resistance has been confirmed, and the presence of MBL has been diagnosed, i.e. * Confirmed by gene testing, or
* Inferred by antibiotic susceptibility testing showing which alternative antibiotics will not work (and which would have worked, if the CR were not MBL)

In the presence of MBL, colistin-based therapies are one of the very few options, typically in conjunction with tigecycline and aminoglycosides such as amikacin. If the infection is an Enterobacterales MBL infection and aztreonam is available, then ceftazidime/avibactam plus aztreonam is an un-licenced combination which may be used. A cefiderocol susceptibility test may be undertaken to confirm that cefiderocol is active prior to treatment initiation.Based on UK epidemiology, most of these cases will be caused by either Enterobacterales or *Pseudomonas spp*.No specific infection site, but characteristically can include the ‘slower’ less critically serious infection sites (e.g. cUTI, some of the pneumonia cases, skin & soft tissue, bone and joint infections, CF, etc) in which there is time to do the testing. 1. **‘Clinically urgent, and suspected CR’ indication**Initiation of cefiderocol therapy when the patient is critically ill and requires immediate effective therapy (i.e. in ICU, where any lack of effect of initial therapy would significantly increase the risk of death), and the infection is highly suspected to be caused by a CR pathogen (i.e. due to risk factors such as patient history/travel, previous failure to treatment with carbapenems, colonization with a of CR pathogen, or local epidemiology of CR pathogens), and there is the potential for rapid worsening.

Due to the severity of the patient’s health, and the importance of effectively treating an unknown infection, combinations of the following treatments may potentially be tried: amikacin; gentamicin; aztreonam; ceftazidime with avibactam; ceftolozane with tazobactam; imipenem with cilastatin and relebactam; meropenem with vaborbactam; piperacillin with tazobactam; colistin, high dose meropenem; tigecycline. In any specific suspected CR case, some of these options may be more/less relevant (e.g. due to specific risk factors).This suspected CR treatment period continues until further testing can inform treatment review (i.e. ‘start smart, then focus’), when the confirmed treatment period starts. If testing confirms suitability of other treatment options, then de-escalation to a more targeted therapy may be appropriate, following stewardship guidelines.Most of these patients will subsequently be identified and confirmed as CR, and a significant proportion will also be identified as pathogens with limited treatment options, as described above.Again, based on UK epidemiology, most of these cases will be caused by either Enterobacterales or *Pseudomonas spp.*Characteristically, the infection sites are serious and ‘faster’ with rapid deterioration – like severe pneumonia or BSI/sepsis – in which rapid time to effective therapy is essential.‘Sequential’ use of cefiderocol may also occur, i.e. when cefiderocol is initiated in the suspected CR setting, and then continued into the confirmed CR setting (e.g. if testing confirms carbapenem resistance and the presence of MBL, or if the toxicity profile of the active therapeutic options would prevent treatment).Selection of two (or more) ‘primary indications’ is aligned with NICE’s HTA process guide for this project (section 4.4a). Furthermore, economic exploration and analyses that can be considered to reflect a range of relevant patient populations and clinical settings would facilitate the subsequent extrapolation of NHB to PNHB. It may also be useful to model more than one infection site, per population.It is important to recognise that any ‘primary indications’ will only represent subsections of the entire ‘full’ eligible patient populations, which are the relevant populations for the PNHB economic extrapolation and analysis. As outlined in the EEPRU report and in NICE’s HTA process guide for this project (section 4.4), the NHB estimated for cefiderocol ‘primary indication/s’ must be multiplied by a patient number estimate that reflects the ‘all eligible’ population, to derive a PNHB figure. Finally, it is also important to recognise that these eligible patient populations may develop over time. As carbapenem resistance increases, the number of patients for whom there are ‘limited treatment options’ will also increase. This needs to be considered – and estimated – over the time period/s for subscription-based payment (i.e. 2022 to 2025/2032) for the PNHB analysis. | Comment noted. The scope needs to cover the entire population for which all relevant evidence will be considered by the evaluation committee, and therefore is broader than the populations likely to be considered as part of the high value clinical scenarios. Defining separate PICOs for the high value clinical scenarios is beyond the scope for this stage but will be undertaken for EEPRU’s protocol development. No action required.  |
| British Thoracic Society  | 1)In CF patients the phrase “infections caused by aerobic gram‑negative organisms with limited treatment options.” Would cover this group. 2)CF patients may have an exacerbation of bronchiectasis with gram negative organisms, without evidence of pneumonia - so this is why point 1 above is important for this group  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | It should be recognised that the marketing authorisation is based on infections that were chosen partly because they presented the easiest way of collecting sufficient numbers of subjects for trials. In clinical practice, infections caused by carbapenem-resistant bacteria will include a range of conditions that will never be studied as part of a randomised controlled trial. Nevertheless, infection specialists will want to use cefiderocol for these conditions. | Comment noted. No action required. |
| NHS England & NHS Improvement | The population definition requires refinement. In clinical practice, cefiderocol is likely to be considered in two settings:1. Patients with severe/life-threatening sepsis or at high risk of mortality (immunocompromised) and with risk factors for a pathogen producing metallo-beta-lactamase:
	1. Previous colonisation or infection with such a pathogen.
	2. Local outbreak of infection with these pathogens.
	3. Repatriation from healthcare setting with high prevalence of colonisation or infection with these pathogens.
2. Patients with known current colonisation/infection with pathogens producing metallo-beta-lactamase and not responding to current therapy.
 | Comment noted. The scope needs to cover the entire population for which all relevant evidence will be considered by the evaluation committee, and therefore is broader than the populations likely to be considered as part of the high value clinical scenarios. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | From discussion in the scoping workshop use for infections due to carbapenem resistant organisms (CRO) seemed mostly likely use. Therefore, should patients with CRO be considered separately? | Comment noted. All relevant evidence will be considered by the evaluation committee including one or more high value clinical scenarios. No action required. |
| MSD  | MSD suggests that the term “limited treatment options” should not only focus on resistance but also pharmacokinetic/pharmacodynamic (PK/PD) considerations such as lung penetration, as PK/PD is an issue of increasing prominence from a regulatory and antibiotic choice perspective. Limited treatment options should also consider contraindications and key adverse events, including issues such as acute kidney injury. | Comment noted. ‘Limited treatment options’ would encompass the reasons for why they are limited and aligns with the wording in the marketing authorisation therapeutic indications. No action required. |
| MSD  | MSD anticipates that the evaluation may primarily follow a pathogen-based approach and therefore suggest that the final scopes should be comparable across both pilot antimicrobials to allow for better comparison and avoid definition solely by the indications in the respective product labels. | Comment noted. NICE can only evaluate a technology within its marketing authorisation. The teams involved in developing the scopes have worked closely together to ensure consistency, where possible. The high value clinical scenarios may differ for each product. No action required. |
| Public Health Wales  | The indication in the MA is for treating infections due an anaerobic Gram –ve organisms in adults with limited treatment options, and as such this is a very wide license, covering both empirical and directed therapy, regardless of the primary site of infection. We are very likely going to use this drug within its’ license in the vast majority of cases. Given this drugs’ unique ability to bypass metallo-beta-lactamases, I would see it being used primarily where the organism and resistance mechanism is already known or strongly suspected, and as such this would be directed therapy, or possibly empirical if suspected infection due to NDM-1 outbreak. Whilst the infection is likely to be picked up through a positive blood culture, and therefore we would be treating bacteraemia, the primary infection source could be anywhere, such as respiratory, urinary, skin and soft tissue, bone, etc., so we will also need to know the penetration into different sites. So to recap, we would be treating a known or highly suspected Gram –ve organism carrying a metallo-beta-lactamase gene, bacteraemia with known or unknown primary source of infection. Less likely is empirical treatment due to an outbreak in ICU caused by the same organism. | Comment noted. All relevant evidence will be considered by the evaluation committee including one or more high value clinical scenarios. No action required. |
| Pfizer Ltd  | No comment | Comment noted. No action required. |

## Section: Comparators

| Consultee/ Commentator | **Comments [sic]** | Action |
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| Shionogi | Comparator selection for the economic analysis will need to be based on the specific ‘primary indication’ population/s, rather than the more general/entire population, as described above.More general comments on the draft list of comparators follow:Treatment will depend on the precise clinical setting (therefore separate comparators should be listed for suspected CR and confirmed CR populations) and a range of factors (infection site, pathogen, mechanism of resistance, patient renal status, local epidemiology etc). In the suspected CR setting, and for patients who have severe infections and/or are critically ill, treatment should be the antibiotic agent/regimen that has the best chance of being effective against the range of likely carbapenem-resistant pathogen types, i.e., the antibiotic regimen with broadest CR coverage. This approach reduces the risk of making a ‘wrong’ selection – i.e. choosing antibiotic therapy against which the pathogen is not sensitive and does not work – and reflects the ‘start smart’ principle. In the confirmed CR setting, information from testing and consequent knowledge/belief on the type of pathogen and resistance mechanism type is available. This allows a more definitive treatment selection to be made, selecting from the list of antibiotic therapies that are known to have activity against that actual causal pathogen– and reflects the ‘then focus’ principle. There is therefore a very long list of potential treatments which might be used across these possible clinical scenarios. This is observed in NHS prescribing, which is extremely variable.The current draft list seems somewhat arbitrary and incomplete, and it is unclear how this list of agents (and combinations thereof) was derived. Some potentially relevant agents (e.g. amikacin, aztreonam) and combinations (e.g. colistin plus tigecycline) are absent. Also, given the focus of this assessment on carbapenem-resistant infections, carbapenem monotherapy agents (e.g. ertapenem and meropenem) are presumably only used at very high doses. The rationale for use of such agents may remain unclear conceptually and NICE should consider carefully whether they are appropriate therapy options and whether they thus remain suitable comparators. We advise that there need to be lists of treatments/comparators for individual clinical scenarios, rather than one list encompassing the range of heterogenous scenarios. For example, the list of treatments that should be used when certain resistance mechanisms - e.g. MBL have been identified, will be very specific – and very small. From a pragmatic perspective, this will be required for NICE’s assessment of certain ‘primary indications’, as described earlier. Furthermore, the list of potential treatments could change, when considering future time horizons and different epidemiology situations. As already highlighted, the UK could likely see MDR, XDR and PDR organisms more commonly, in a similar manner to much of Europe, and therefore the number of treatment options lessen. | Comment noted. The scope has been amended to cover the broad range of possible comparators used in clinical practice. As the comparators are likely to differ according to clinical scenario (for example, comparators for ‘empiric’ treatment options will differ from those with directed treatment after microbiology results are obtained), the final scope has been amended to reflect this. The consideration of comparators at the scoping workshop has been captured and will be very helpful in specifying the high value clinical scenarios for detailed study. |
| British Thoracic Society  | Yes – in CF combination therapy of the comparators listed are used- not just meropenem and Tobramycin, but other combinations of drugs listed | Comment noted. See the response to the comment on comparators by Shionogi. |
| British Society for Antimicrobial Chemotherapy | * With regard to the treatment of ESBL or AmpC-producing Gram negative bacteria, temocillin is a relevant comparator that should be included in the list
* The term “best alternative care” is a tenuous description because the evidence base to support their use is generally limited to case-series, so claiming superiority or best care is untested. This is illustrated by the diversity of treatment regimens that were included in the best alternative care arm of pivotal trials.
 | Comment noted. See the response to the comment on comparators by Shionogi. |
| NHS England & NHS Improvement | The list of comparators most likely to be active against metallo-beta-lactamase producing organisms is:* Tigecycline
* Colistin
* Aztreonam in combination with ceftazidime-avibactam

Other comparators that may be active are:* Amikacin
* Fosfomycin
* Ciprofloxacin

Consider adding co-trimoxazole for its activity against Burkholderia and Stenotrophomonas species.Other drugs should be removed from the list of comparators in the draft scope. | Comment noted. See the response to the comment on comparators by Shionogi. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Limited use of therapy for resistant Gram-negative infections in Scotland and would always be directed by ID/Micro advice.Meropenem +/- aminoglycoside (gentamicin or amikacin) or aztreonam most likely treatment.If required then colistimethate sodium (colistin), alone or in combination with fosfomycin or meropenem.Low use of newer combination products in Scotland.Co-trimoxazole used for Burkholderia infections | Comment noted. See the response to the comment on comparators by Shionogi. |
| MSD  | MSD considers the list of comparators to be comprehensive, except for two omissions: temocillin (covers *Klebsiella pneumoniae carbapenemases* (KPCs) in urinary tract infections (UTIs) and, as a narrow-spectrum penicillin, may be considered to carry particular value in antimicrobial stewardship, or AMS) and amikacin. | Comment noted. See the response to the comment on comparators by Shionogi. |
| Public Health Wales  | As mentioned in the meeting, there are virtually no options for treating NDM carrying organisms, so treatment / comparators fall to combination regimes involving high dose carbapenems in combination with amikacin or other combinations, with choice and dose driven by PK/PD modelling. | Comment noted. See the response to the comment on comparators by Shionogi. |
| Pfizer Ltd  | Pfizer suggests that this section is divided into two separate sections:* Empirical comparators - where there is a vast amount of options and therefore not all likely to be suitable for the economic modelling
* Confirmed comparators - where there are more limited treatment options, and therefore more suitable for economic modelling

Based on marketing authorisation Pfizer expects most relevant comparators to be those identified for use in a confirmed resistance setting. The empirical setting may be suitable in situation that is informed by the presence of risk factors or other information that suggest a high risk of MDR infection. However, options in these areas are limited. | Thank you for your comment. The scope has been amended to cover the broad range of possible comparators used in clinical practice. As the comparators are likely to differ according to the clinical scenario (for example, comparators for ‘empiric’ treatment options will differ from those with directed treatment after microbiology results are obtained), the final scope has been amended to reflect this. The consideration of comparators at the scoping workshop has been captured and will be very helpful in specifying the high value clinical scenario(s) for detailed study. |

## Section: Outcomes

| Consultee/ Commentator | Comments [sic] | Action |
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| Shionogi | This question needs to carefully consider the distinction between measures, benefits and outcomes and what is valid/applicable for each of the populations included (i.e. suspected and confirmed CR). The most appropriate measure of treatment effect is likely to be a combination of trial evidence (using ‘cure-focused’ endpoints, which were the primary measures for all cefiderocol trials), and **in vitro susceptibility/activity data**. The trial data is limited for various reasons, e.g. due to nature of study population, comparator agents used, sample size and statistical design. In particular, trials in this therapy area are designed to demonstrate non-inferiority and typically assess efficacy against carbapenem-sensitive pathogens, and only include pathogens/mechanisms of resistance for which the new drug is active (i.e. the pathogen mix is different for each drug, which prevents standard NMA approaches to anti-infectives). This means that estimates of relative treatment effect and benefit, for the treatment of carbapenem-resistance pathogens in certain specific clinical settings may have to rely on the in vitro evidence base. Susceptibility data for surveillance studies provides important information on the activity profiles of different antibiotics. In the absence of susceptibility testing results in the clinical setting (i.e at the ‘suspected’ stage), this data is a key measure informing likely treatment effect. This measure is highlighted in the EEPRU report and the NICE HTA process document and should therefore be added to the list of Outcomes. | Comment noted. All relevant evidence will be considered by the evaluation committee. No action required. |
| Shionogi | **All-cause mortality** (and including 90-day mortality) is not appropriate as a measure of relative treatment effect, as it is confounded and thus poorly correlated with the effect of treatment of the original infection. Considering that these are nosocomial infections, and as such the primary diagnosis that lead the patient to the hospital in the first place was not the infection, all-cause mortality rates are confounded, particularly over longer time periods. They are poorly correlated with the effect of treatment of the original infection, especially as time progresses, due to other determinants of mortality (e.g. new/secondary infections, background condition/s, etc.). Similarly, very immediate mortality rates are likely to be poorly correlated with treatment, which need approximately 48 hours to take effect and have an impact on the infection and are more likely to be determined by pre-existing co-morbidities.Nevertheless, treatment-related mortality is of course a relevant outcome for economic modelling. This can be best estimated by extrapolation from suitable measures of treatment effect, e.g. clinical cure (see below). | Comment noted. The outcomes section of the scope has been updated to remove 90-day mortality. |
| Shionogi | **Clinical cure** (i.e. complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy was needed) is relevant as it is the most direct and suitable measure of treatment effect from trials. The EEPRU report describes certain limitations of clinical trial evidence in this therapy area, highlighting that antimicrobial trials are typically designed/powered to demonstrate non-inferiority. Furthermore, the primary objective that these trials are designed to assess is clinical cure (of infection), e.g. as measured by ‘test of cure’ endpoint. Such cure-focused evidence is thus a better measure of relative treatment effect than mortality evidence from trials. Clinical cure (e.g. at ‘test-of-cure’, as used in the majority of the clinical trials including CREDIBLE, either as a primary or secondary endpoint) is also a good proxy for the most relevant survival outcomes, i.e. incremental survival dependent on successful treatment of the original infection. Given the potentially confounded nature of mortality endpoints described below, we suggest that this is a ‘purer’ and more direct measure of relative treatment effect. Clinical cure can thus be used as the efficacy input for economic modelling, to isolate treatment effect, with downstream impacts on other outcomes (e.g. survival, Hr-QoL, and HCRU/costs) estimated using sources of data not limited to clinical trials. | Comment noted. No action required. |
| Shionogi | **Microbiologic eradication** is relevant as it may be another indicator of treatment effect, similarly to clinical cure as described above. However, it can be confounded by the presence of other organisms, unrelated to the treatment of the original infection. | Comment noted. No action required. |
| Shionogi | **Time to effective therapy** is an important measure in the ‘suspected’ clinical setting. It is a determinant of outcomes such as mortality and has an impact on NHSS HCRU/costs. | Comment noted. As stated in the NICE methods guide, resource utilisation and costs will be included in the analyses and considered by the evaluation committee. All-cause mortality is included within the outcomes list in the scope. No action required. |
| Shionogi | **Emergence of resistance** is relevant. However, this will be difficult to estimate. Also, there may be different forms of emergent resistance to consider, i.e. cross-resistance | Comment noted. No action required. |
| Shionogi | **Hospital days** is relevant as this directly links to HCRU and other factors which potentially drive the value. | Comment noted. No action required. |
| Shionogi | **Intensive care unit (ICU)** days is relevant, for the same reason as hospital days, as described above. Many of the patients suitable for cefiderocol will be treated in ICU and this directly links to HCRU and other factors which potentially influence value. | Comment noted. No action required. |
| Shionogi | **Readmission date within 90 days** of treatment is not appropriate as a measure of relative treatment effect, for the same rationale as 90-day mortality, as described above. 90 days is too long to measure treatment effects due to many confounding factors in this clinical setting and over this time period. | Comment noted. The list of outcomes in the scope is inclusive so re-admission date has been included. No action required. |
| Shionogi | **Health-related quality of life** (HrQoL) is relevant. | Comment noted. No action required. |
| Shionogi | **Adverse events** are relevant, as they have direct impacts on both HrQoL, plus HCRU and costs. | Comment noted. No action required.  |
| Shionogi | **Renal impairment** associated with colistin-based therapies will be particularly relevant for this assessment, since this is known to have a significant impact on HrQoL and costs. | Comment noted. No action required. |
| Shionogi | All **NHS HCRU and costs** are important to capture for the economic analysis. | Comment noted. As stated in the NICE methods guide resource utilisation and costs will be included in the analyses and considered by the evaluation committee. No action required. |
| Shionogi | The **time horizon** **for patient-level NHB** economic modelling should be lifetime.The **time horizon for population-level epidemiology** and modelling of the additional value elements (e.g. insurance, transmission, diversity, etc.) should be at least 10 years. | Comment noted. As stated in the NICE methods guide, time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. No action required. |
| Shionogi | A range of other measures/benefits/outcomes may also be relevant, particularly to assess the additional antibiotic value elements proposed by EEPRU/NICE.* **Enablement**, i.e. having a satisfactory health status and thus able to receive other medical care (e.g. chemotherapy or surgery), is another relevant outcome.
* **Transmission and outbreaks**, i.e. an estimate of the likelihood of transmission of infection (particularly transmission of resistant strains and DNA between strains) from one patient to others – and potential generation of outbreaks within hospitals - is another relevant outcome.
 | Comment noted. These outcomes should be incorporated within those detailed in the scope such as microbiologic eradication and clinical cure. No action required |
| Shionogi | Specific epidemiology estimates will be required for the economic analysis, and it may be helpful to list these in the Scope, perhaps in this Outcomes section. | Comment noted. The scope contains a list of outcomes but not at this level of detail. No action required.  |
| Shionogi | For all outcome measures included in the final scope, it would be helpful to describe why they are relevant and how they will be incorporated within the economic model and/or wider consideration of value. For example, ‘days in hospital’ could be important per se because of the HCRU or disutility associated with being in hospital, or it might be a proxy for treatment effectiveness, or it may be a determinant of transmission value. Different outcomes may be relevant for the suspected, and confirmed, settings. | Comment noted. The scope contains a list of outcomes but not at this level of detail. No action required. |
| British Thoracic Society  | In CF - outcomes such as reduction in exacerbation rate may also be used | Comment noted. No action required.  |
| British Society for Antimicrobial Chemotherapy | Infections caused by multi-drug resistant bacteria are often acquired in hospital. Patients with hospital-acquired infections are often more frail, have a greater number of co-morbidities and consequently a worse outlook compared with the average patient even before they acquire a healthcare infection. Consequently, modelling assumptions should try to identify these poorer prospects when addressing the likely value of these antibiotics to the NHS.  | Comment noted. No action required. |
| NHS England & NHS Improvement | Suggest the following additional outcomes:* Length of antibiotic treatment
* Clostridioides difficile infection
* Eradication of colonisation (3% of dose excreted via intestine so may impact colonisation)

In vitro susceptibility data | Comment noted. The outcomes section of the scope has been updated accordingly. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Adverse events should be divided into drug reactions and patient toxicity.C. difficile is a particular concern with cephalosporins so suggest capture this as a key adverse event. | Comment noted. The outcomes section of the scope has been updated accordingly. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Potential additional outcomes could be treatment failure (requiring change of treatment) and emergence of resistance to Cefiderocol. | Comment noted. The outcomes section of the scope has been updated accordingly |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Environmental cost of the antibiotic (pollution of the environment during the manufacturing of the antibiotic and residue of the antibiotic and its metabolites following excretion) - part of National Action Plan. Delivery Programme 4 – Minimise spread of AMR through the environment. | Comment noted. Environmental costs are not within the remit of the assessment. No action required. |
| MSD | The proposed outcome of 90-day readmission rates could perhaps be divided into two categories, namely, 90-day ITU readmission and 90-day hospital readmission. | Comment noted. The outcomes section of the scope has been updated to remove 90-day mortality because this will be taken account of in the all-cause mortality outcome. |
| MSD  | MSD would also suggest that the outcome “emergence of resistance” be extended to include superinfections (e.g. increased incidence of *C. difficile* infection, methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) as antibiotic use can have wider consequences). | Comment noted. All relevant forms of resistance will be included in the analyses and considered. No action required |
| Public Health Wales  | As well as the obvious outcome measures such as all-cause mortality (at 30 days as well as 90), clinical cure (which also needs to be defined – such as resolution of symptoms and no reoccurrence within 30 days?) and microbiological eradication, there also needs to be a recognition of the adverse effects and unintended consequences. This includes the development of resistance to this drug, driving cross resistance in other drug/bug combinations, increased prevalence of HCAIs (especially CDI), selecting out other resistant organisms, drug toxicity and both dose-related and idiosyncratic adverse drug reactions, drug interactions and physiological interactions. | Comment noted. The outcome adverse events is listed in the scope. No action required. |
| Pfizer Ltd  | Yes, we agree with the proposed outcomes, however, have the following amends:Additional wording:Pfizer would add that there should be specific reference to relevant outcomes being captured at both a population and individual level where appropriate This includes factors such as population resistance to modelled antibiotics, total country resistance, population level- mortality, number of hospital days for example. This list is not exhaustive.  | Thank you for your comment. No action required. |
| Pfizer Ltd | Additional Outcomes:We propose the suggested inclusion of additional outcomes to capture specific stewardship activities such as:* Number of antibiotics used in treatment cycle
* Number of appropriate treatment options given infection(s)
* Number of days of therapy

In addition, resistance / epidemiology market outcomes should be considered for inclusion:* Resistance markers: markers of population resistance / Number and severity of hospital outbreaks
 | Thank you for your comment. The outcome emergence of resistance is listed in the scope. No action required |
| Pfizer Ltd  | Change to existing outcomes:“90-day mortality” Be changed to:“Annualised, 14-day and 28-day mortality” Annualised mortality allows uniform modelling and comparison of interventions. However, it is important to consider shorter measures of mortality including, day and 28-day mortality at least in communicating to the wider stakeholder community. Shorter periods of mortality are more aligned to outcome measures used in the clinical trials and are more relevant clinically. It is important to note that mortality to the infection decreases significantly as time progresses. 28-day / 14-days is more relevant to microbiological eradication/test of cure and mortality outcomes. Pfizer does recognise that longer term mortality should be considered as part of the expected extended time horizon of the modelling.  | Thank you for your comment. The outcomes section of the scope has been updated to include days of therapy. |

## Section: Economic analysis

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Shionogi | The primary consideration should be clinical need (i.e. at the individual patient level). From this clinical perspective the proposed criteria to identify the “primary” indication(s) should be:* Availability of alternative treatments - defined as the availability of treatments that are safe and active against the pathogen (and its resistance mechanisms) causing the resistant infection - which directly links to unmet need
* Disease severity and patient’s underlying health status

These factors will determine the patient level benefit (and NHS HCRU/cost savings). For example, the benefit of using an effective antibiotic for a patient with a life-threatening infection for which there are no effective alternatives will obviously be high. Another clinically high value scenario may arise when there is an alternative treatment which is efficacious but with significant adverse events and limitations in dosing (e.g. colistin). We suggest that there should be at least one primary indication selected for each of the two – i.e. suspected and confirmed – clinical settings. Without at least two populations prioritised for in-depth analysis, any efforts to extrapolate per patient health benefit to the wider population of relevance are likely to be flawed as there will be little to inform which range of values should be applied. If there are multiple indications with similar patient level benefit, then absolute patient numbers may be relevant criteria to prioritise the primary indication/s. In conclusion, we propose that the primary consideration for identifying these indications should be clinical need, i.e. the specific scenarios in which cefiderocol will be ‘reached for’ by doctors, in both the suspected, and the confirmed setting. The relative frequency of scenarios within these two settings should be a secondary factor when considering a clinical perspective. Ideally, the two (or more) primary indications would feature a combination of both, i.e. an area of high unmet need which arises frequently.The proposed two ‘primary indication’ population descriptions are provided in the Population section above. | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. No action required. |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | * The unique selling point of this antibiotic is its activity against metallo-carbapenemases. No alternative treatments exist that have this activity. Consequently, treatment of infections caused by bacteria producing metallo-carbapenemases should be the primary indication used in the economic analysis.
* Activity of cefiderocol against serine-carbapenemase-, ESBL- or AmpC-producing bacteria is not novel; there are a number of other beta-lactam and non-beta-lactam antibiotics that work equally well against these bacteria
 | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios.  |
| NHS England & NHS Improvement | Suggest modelling for two populations described above:1. Directed Empirical Therapy Strategy - Patients with severe/life-threatening sepsis or at high risk of mortality (immunocompromised) and with risk factors for a pathogen producing metallo-beta-lactamase:
	1. Previous colonisation or infection with such a pathogen.
	2. Local outbreak of infection with these pathogens.
	3. Repatriation from healthcare setting with high prevalence of colonisation or infection with these pathogens.

This directed empirical therapy strategy would result in discontinuation of cefiderocol if a pathogen sensitive to suitable alternative agents was cultured or continuation of cefiderocol if a pathogen sensitive only to cefiderocol was cultured (or alternative agents were contra-indicated for any reason).Pathogen-Directed Strategy - Patients with known current colonisation/infection with pathogens producing metallo-beta-lactamase and not responding to current therapy. | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Infecting organism as informed by clinical experts and scoping consultation.Environmental cost of the antibiotic manufacture and excretion (see above). | Comment noted. No action required. |
| MSD  | The inclusion of one or more primary indications in this evaluation could compromise the ability of the economic analysis to fully focus on what is of greatest value to the NHS in terms of overall unmet need and morbidity/mortality. For example, bacteraemia or a key indication such as hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP, with or without bacteraemia), would provide a more robust measure of value to the NHS than relatively “high-volume” infections such as UTI or a very common pathogen such as *E. coli*. | Comment noted. All relevant evidence will be considered by the evaluation committee including one or more high value clinical scenarios. No action required. |
| Public Health Wales | No comment  | Comment noted. No action required. |
| Pfizer Ltd  | **Additional Value Elements:**Pfizer would like to see the inclusion of productivity value as one of the additional value elements given the wider population benefit antibiotics bring to society and thus the impact on productivity at a population level.  | Thank you for your comment. The NICE methods guide does not require the inclusion of productivity value. As productivity value is not unique to antimicrobials it cannot be considered in the evaluation. No action required |
| Pfizer Ltd | **Threshold:**We would recommend the following wording: **“In the base-case analysis, a threshold of £20,000 per quality-adjusted life year should be used for the calculation of net health benefits.”** Be changed to:**“flexibility will be applied to the QALY range threshold of £20,000-£30,000 as the base case, to ensure that the new approaches to valuation that may evolve in the future are appropriate to meet the overarching aims of the project and stimulate future research and development.”** This is to ensure that the overall aims of the project are not restricted by an imposed WTP threshold. In addition, the update to the NMR which reviews modifiers; severity of illness, innovation/ unmet need and uncertainty, should also be considered. Wording highlighted under the background section (page1) clearly emphasises the importance of severity of illness with wording such as;  **“These pathogens are multidrug-resistant Gram-negative bacteria that can cause severe infections in secondary care settings”** and **“For severe and life-threatening infections,”,** along with also highlighting the need for innovation **“new antimicrobials are urgently needed”** – Suggesting that there could be an overlap with workings being undertaken as part of the NICE methods review to ensure the existing QALY threshold does not become a significant burden on the valuing of medicines and limiting access for patients.  | Thank you for your comment. Sensitivity analyses will be performed for different thresholds (£15,000 and £30,000 per quality-adjusted life year) but the base-case analysis will be at £20,000 per quality-adjusted life year. No action required. |
| Pfizer Ltd  | **Primary Indication:**Pfizer’s view is that the criteria outlined to identify the primary indication should also include that of Real-World Evidence where plausible. In addition, the criteria used to identify the primary indication should be dependent on the antibiotic and the proposed positioning or value it offers to society. Therefore, all criteria should be used as part of the assessment with consideration taken as to which is the most relevant for the antibiotic in question.Cefiderocol is licenced for where there are limited treatment options with suspected of confirmed multidrug resistance gram-negative infections. With reference to “primary Indication” being modelled; Pfizer would like to see all licenced indications modelled within the main economic model, with the ambition to cover all key indications to ensure the economic model more accurately reflects the population net health benefit. An approach to modelling which considers multiple indications and pathogen combinations including several considerations to EEPRU’s value framework has been demonstrated in publications1, thereby demonstrating plausibility. Sequentially, a more pragmatic approach to other indications can be taken where there is less available data, whereby Pfizer would like to see a large emphasis on the mitigation of uncertainty through expert elicitation and a practical yet novel approach to the revising of value based on gaps in data for modelling.References:1.Gordon J, Darlington O, McEwan P, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38(8):857-869. doi:10.1007/s40273-020-00906-6 | Thank you for your comments and reference. All relevant evidence will be considered by the evaluation committee. No action required. |

## Section: Equality and Diversity

| Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- |
| Shionogi | No comments  | Comment noted. No action required. |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comment | Comment noted. No action required. |
| NHS England & NHS Improvement | Children and pregnant women excluded due to licence restrictions. | Comment noted. NICE must provide recommendations within the marketing authorisation. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | No issues identified. | Comment noted. No action required. |
| MSD | No comment  | Comment noted. No action required. |
| Public Health Wales  | No comment | Comment noted. No action required. |
| Pfizer Ltd | No comment  | Comment noted. No action required. |

## Section: Other considerations

| Consultee/ Commentator | **Comments [sic]** | Action |
| --- | --- | --- |
| Shionogi | How do EEPRU/NICE plan to extrapolate from NHB estimates (generated from the ‘primary indication/s’ analyses) to PNHB estimates? This remains unclear, and again, key to this task will be:* epidemiology data, and
* more than one in depth analysis (in order to inform the range of NHB per patient applied to the wider eligible populations).
 | Comment noted. The EEPRU report (2018) and the Evaluation Framework provide more detail on how the value might be estimated in the analyses. No action required. |
| Shionogi | The additional antimicrobial value elements proposed by EEPRU/NICE need to be considered carefully, and do not appear (explicitly) in the draft Scope. It would be helpful to describe NICE/EEPRU’s intended framework and approach to incorporating these analyses in the Scope. Whilst EEPRU/NICE have outlined a range of additional value elements at a conceptual level, these remain poorly defined at the operational level. This area of work is likely to be complex and quite challenging; for example, it may involve predicting future clinical scenarios and patient populations which differ significantly from those described in the draft Scope. As highlighted earlier, substantial epidemiological work will likely be central to this, which could be usefully be outlined in the Scope (for example, in the Outcomes section).Additional value elements that should be considered for cefiderocol include:* Enablement and transmission value. Cefiderocol will provide more effective therapy in certain cases and could thereby reduce infection management time in hospital, either due to reduced time to effective therapy in the suspected setting, and/or due to reduced time managing colistin renal toxicity in the confirmed setting. Therefore, enablement value and transmission value will both be relevant, since both these benefits are dependent on the duration of time that patients are managed with infection.
* Insurance value. Cefiderocol has a comprehensive activity profile against various forms of Gram-ve pathogens and CR resistance mechanisms, plus activity against other types of (non- CR) resistance. Therefore, the potential insurance value will be substantial, particularly if resistance against alternative therapies is anticipated to significantly increase and new areas of high unmet need emerge.
* Diversity value. Cefiderocol will contribute to diversity value. Its use in place of other agents will reduce resistance selection pressure on those agents. Furthermore, in the ‘suspected’ setting, the broader Gram-ve activity profile of cefiderocol (and thus greater probability of providing effective therapy quickly) will reduce antibiotic ‘wastage’ (i.e. inadvertent use of ineffective therapies).
 | Comment noted. The section ‘Economic Analysis’ lists the additional value elements. No action required. |
| Shionogi | The proposal to use a threshold of £20,000/QALY should be modified to allow the committee to explore cost-effectiveness and value according to the standard NICE reference case of £20,000-30,000/QALY, in line with the current NICE Methods Guide and therefore other NICE decision-making. This is particularly valid given these key considerations:* Severity of these patients’ condition and high level of unmet need. The draft Scope refers to ‘severe and life-threatening infections’ and describes how ‘new antimicrobials are urgently needed’.This would be in line with existing decision modifiers (e.g. the end-of-life policy) and with anticipated revisions to the NICE methods, which will explicitly attribute additional value to health gain (or increase the willingness-to-pay threshold) in particularly severe conditions.
* Uncertainty. NICE have acknowledged that for these pilot assessments of new antimicrobials, there will be inevitable uncertainty in the evidence base and estimates of health gain, requiring a pragmatic stance on uncertainty. Such a stance would also be in line with anticipated revisions to the NICE methods, which will recommend a greater tolerance of uncertainty. Accordingly, the operation of a single £20,000/QALY threshold due to concerns about uncertainty would be inappropriate.
* The innovative nature of the technologies being assessed. The need for new antimicrobials has been recognised, and the project for which this new NICE methodology is being piloted (i.e. the subscription-based payment system) was developed in direct response to that policy imperative. It is therefore particularly important that any HTA evaluations done for new antimicrobials avoid the risk – and consequences of – undervaluing their benefit.
* Furthermore, the willingness-to-pay threshold used for this pilot project should not inadvertently act as a barrier to achieving one of the main policy objectives, i.e. to determine a fixed (subscription) payment amount, that will provide an incentive to spur increased R&D investment into this therapy area. It would therefore be sensible for NICE – and their Appraisal Committee – to take a flexible approach to cost-effectiveness thresholds in this case.

The potential timescales for subscription-based payment contracts may be a relevant consideration for the NICE assessment and outputs. For example, the average annual value may differ over years 1-3, compared to years 1-10, due to changing epidemiology.  | Comment noted. Sensitivity analyses will be performed for different thresholds (£15,000 and £30,000 per quality-adjusted life year) but the base-case analysis will be at £20,000 per quality-adjusted life year. No action required. |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comment | Comment noted. No action required. |
| NHS England & NHS Improvement | No comment | Comment noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Stewardship approach in Trusts with respect to approval for use. In Scotland agents for treatment of serious/resistant Gram-negative infections would be used on specialist ID/Micro advice only. | Comment noted. No action required. |
| MSD | No comment | Comment noted. No action required. |
| Public Health Wales  | The main indication has previously been described as treating Gram –ve organisms carrying the metallo-beta-lactamase gene with known sensitivities, usually identified in blood culture with a primary site of infection at any body site. As such, a detailed understanding of PK/PD and penetration to all bodily sites is needed to understand how effective this drug will be in treating different primary infections. In the workshop, some experts considered using this drug *empirically* in patients at high risk / suspicion of the same organism, or other highly resistant Gram –ve organisms. Bronchiectasis and CF were also mentioned. Given how unusual this drug is, this increased use raises the question of how we measure effect in this wider population against risk of developing resistance to this drug earlier, and the population benefit of each set of uses. Directed therapy vs the concept of diversity also drives the question of development of resistance in this one drug vs development of resistance across a range of last line agents at a much lower overall rate. Again, this could be modelled.  | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required |
| Public Health Wales  | In terms of economic analysis, some experts were considering not using this drug due to its high cost, however the subscription model raises other issues. First of all, you are now comparing a drug which is free (to the prescriber) to comparator drugs with potentially very high acquisition costs. One potential outcome is that this drug, if made freely available with a wide range of options, could be used more, not less, than originally intended, leading to earlier resistance. Another consideration is that this drug is likely only going to be used once a resistance mechanism is known, with the result that it could take up to a week before treatment with this drug could start. Therefore, the balance here is preserving the efficacy of this drug against using it empirically with an associated decrease in morbidity and mortality. Stewardship tools include restricting this drug for micro and ID use only, strict agreed indications, possibly for known Metallo-beta-lactamase producer only, stock restriction by pharmacy with release of stock by micro/ID, use of biomarkers such as procalcitonin to de-escalate treatment. | Comment noted. The use of a subscription model will not mean that the drug will be used in the NHS free of charge; there will still be a transaction cost for the purchase of the drug through the normal supply chains. No action required. |
| Pfizer Ltd | No comment.  | Comment noted. No action required. |

## Section: Questions for consultation

| Consultee/ Commentator | **Comments [sic]** | Action |
| --- | --- | --- |
| Shionogi | Q3. Do established treatments differ according to infection site in people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?Response:As described in response to Q2, the primary determinant for treatment selection should be likelihood of effectiveness against the resistant pathogen causing the infection.Nevertheless, there may be other factors that affect the treatment choice depending on the sites of infection, i.e.* Correlations between pathogens and infection sites, which could result in an indirect impact of infection site on treatment selection.
* Some treatments have regulatory approval for certain infection sites, while others have more pathogen-focused indications. This will be of decreasing importance as pathogen-focused labels become the regulatory standard.
* Differences in tissue penetration – and thus antibiotic in-vivo effectiveness – which is a relevant consideration. However, the essential determinant in such situations remains, i.e. the likelihood of effectiveness against the specific pathogen.

Finally, as described in response to Q1, treatment selection – particularly in the suspected CR setting - may be influenced by severity of infection. Different infection sites may be associated with varying degrees of severity, and thereby influence treatment. But given the defined ‘population/s’ (i.e. those with severe infections), a degree of severity – at least in the suspected setting (see our caveat about this in response to Q1) - can be assumed already.  | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required. |
| Shionogi | Q6. What testing strategies are used in clinical practice for people with severe infections due to aerobic gram-negative bacteria where resistance is suspected?Response:As outlined above, and in ‘Start Smart, then Focus’ guidelines, testing is initiated as soon as possible in severe infections. This is followed by clinical review and potential re-selection of more appropriate therapy. In the NHS, this typically comprises ‘panel’ testing, which exposes samples from the infected patient to a range of antibiotics to assess which antibiotics the pathogen causing that infection is likely to be susceptible to. ‘Gene’ testing may also be done, particularly if resistance levels are high; this aims to identify characteristics of the pathogen – including type of resistance mechanism. | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required. |
| Shionogi | Q8. What stewardship scenarios are relevant to be considered in the analysis? Response:The regulatory indication for cefiderocol – i.e. recommending use when there are limited treatment options – is intrinsically aligned with basic antibiotic stewardship principles.Furthermore, the proposed positions described above for cefiderocol, are aligned with good stewardship principles. The wide and specific Gram-negative activity profile of cefiderocol makes it an ideal antibiotic to use within the suspected setting in line with the ‘Start Smart’ approach for suspected CR infections, followed by de-escalation when appropriate. The same wide activity profile – with activity against ‘difficult’ pathogens (e.g. MBLs) – makes is suitable for specific areas of confirmed use, i.e. for the ‘Then Focus’ stage.To preserve the value of cefiderocol in treating infections against which other agents are ineffective, Shionogi recommend a conservative approach to its use within any ‘cycling’ strategies. ‘Cycling’ is probably only appropriate in certain clinical scenarios, where multiple antibiotic therapies within that restricted population are suitable options (e.g. KPC producing Enterobacterales); it could be considered inappropriate (or not even impossible) when there is a single ‘best’ antibiotic therapy option.  | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required |
| Shionogi | Q10. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Response:The availability of testing (access to suitable tests, and speed of test results retrieval) can clearly influence antibiotic prescribing in both the suspected and confirmed settings.Clinical habits may be slow to change. For example, the ‘Start Smart, then Focus’ approach may represent a shift from historical approaches based on empiric prescribing of inexpensive older antibiotics rather than use of newer, potentially more effective agents, early in the treatment pathway. | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required. |
| British Thoracic Society  | No comment  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | * Limited treatment options should restrict use to infections where at a maximum only two other antibiotics are reasonable options, based on pharmacodynamic factors (antibiotic susceptibility) pharmacokinetic features (site of infection, patient administration options, metabolism or excretion considerations) or patient factors (adverse reactions).
* Piperacillin-tazobactam and meropenem are antibiotics that are frequently used for the treatment of multi-resistant bacteria. Other established choices include aminoglycosides (gentamicin, amikacin, tobramycin), colistin, tigecycline, temocillin, used either singly or in combination
* Generally, treatment options are the same for most infection sites, partly based on good PK/PD characteristics and partly because of limited alternatives.
* Primary indication should include the criterion that this antibiotic is a scare and valuable resource that will become less effective if/when resistance to the antibiotic emerges and that resistance emergence will be accelerated by increased use.
* Highest value indication for cefiderocol is treatment of infection caused by metallo-carbapenemase-producing bacteria. Important comparators are: for KPC – ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam. For OXA-48 – ceftazidime-avibactam. Other antibiotics may be effective on a case-by case basis, according to susceptibility testing results.
 | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. All relevant evidence will also be considered by the evaluation committee. No action required. |
| British Society for Antimicrobial Chemotherapy | * Testing strategies are based on EUCAST criteria (see <https://www.eucast.org/clinical_breakpoints/> ) and 8. UK Standards for Microbiology Investigations. Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases). 30 September 2020. Available from: <https://www.gov.uk/government/publications/smi-b-60-detection-of-bacteria-with-carbapenem-hydrolysing-lactamases-carbapenemases> .
* Stewardship scenarios vary widely from hospital to hospital. However, an essential stewardship feature that should be required under the delinkage scheme is the need for prior authorisation from an infection expert before the drug can be prescribed/dispensed.
* An important barrier to adoption is the availability of rapid identification of carbapenemase. Not all labs currently have access to PCR tests for this.
 | Comment noted. Thank you for the website references. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. No action required. |
| NHS England & NHS Improvement | No comment | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. Does the population reflect those that would be eligible to receive cefiderocol in the NHS in England? a. The marketing authorisation for cefiderocol includes people ‘with limited treatment options’. How is ‘limited treatment options’ defined in practice? Does it refer to severe infections where resistance is suspected/confirmed, or is there a differentiation between the two terms?As mentioned previously patients with other types of infection (CF, bronchiectasis) should be included.Limited treatment options could reflect patient factors such as renal impairment, as well as previous treatments used and prior/history of resistant infections. | Comment noted. All relevant evidence will also be considered by the evaluation committee. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 2. Which treatments are considered to be established clinical practice in the NHS for people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?Already answered. | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 3. Do established treatments differ according to infection site in people with severe infections due to aerobic gram-negative bacteria where resistance is confirmed/suspected?Yes, depends on the ability of an antibiotic to penetrate the infected tissues.  | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 4. What criteria should be used to identify the primary indication(s) for the economic analysis? a. For example: unmet need, disease severity, absolute patient numbers, availability of alternative treatment(s). Are there any others?For an explanation of the “primary” indication(s), please refer to the ‘economic analysis’ section of the table above, and paragraphs 4.3 and 4.4 of the Evaluation Framework.In addition to the greatest unmet need and benefit to public health the primary indication should be reflective of the experts views otherwise the population for the HTA evaluation will be drawn into question.Consideration should be given to the quality and quantity of evidence available to produce robust estimates of population health benefit when selecting the primary indication(s).Environmental impact (see above in Outcomes). | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 5. In which indication(s) is cefiderocol expected to have the highest value when considering the criteria listed under question 4.a?a. What are the most important comparators for this indication(s)?Already answered | Comment noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. What testing strategies are used in clinical practice for people with severe infections due to aerobic gram-negative bacteria where resistance is suspected?

1) Empirical diagnosis and risk assessment on the likelihood of infection with a multi-resistance pathogen based on individual’s past microbiological history, local epidemiology and whether associated with an outbreak.2) Laboratory results from clinical specimens such as blood cultures, swabs. | Comment noted. NICE and EEPRU will be considering all relevant criteria when identifying the high value clinical scenarios. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. Are the outcomes listed appropriate?

Yes | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. What stewardship scenarios are relevant to be considered in the analysis?

Directed useRisk-based empirical use | Comment noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed evaluation and scope may need changing in order to meet these aims. In particular, please tell us if the proposed evaluation and scope:
* could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Cefiderocol is licensed;
* could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
* could have any adverse impact on people with a particular disability or disabilities.
 | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.No issues identified. | Comment noted. No action required.  |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | 1. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

Yes, not all automated susceptibility testing platforms include Cefiderocol. Therefore, additional testing required adding delay and cost into the system. Not all laboratories currently have the ability to detect CROs. | Comment noted. No action required. |
| MSD | No comment  | Comment noted. No action required. |
| Public Health Wales  | No comment | Comment noted. No action required. |
| Pfizer Ltd | **Question 1)**Yes, wording the population is reflected accurately.A) Limited treatment option indication, as referred by emea1, refers to antibacterial agents or combinations expected to be clinically active against multidrug-resistant organisms (resistant to one or more classes of antimicrobial agents) for which there are limited licensed treatment options.Limited treatment options may arise due to resistance to existing treatment options or tolerability/toxicity problems determined by patient and microbiological factors: 1. Resistance (microbiological factors). For example, an option for treating confirmed resistant infection where options are exceedingly limited.
2. Tolerability (patient factors). This may arise for example due to renal impairment; management options become limited in spite of putative antibacterial activity. In this example, the use of potential nephrotoxic agents (e.g. colistin and aminoglycosides) should be avoided leading to a limitation of available treatment options.

**References:**1.European Medicines Agency (EMA); Guideline Evaluation of medicinal products indicated for treatment of bacterial infections. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3\_en.pdf , (07 Jan 2021, date last accessed). | Thank you for your comments and references. No action required. |
| Pfizer Ltd  | **Question 2)****Confirmed resistant pathogen infection:** Antibiotic management of confirmed resistance would be guided by the microbiological sensitivity results obtained from such. The mechanism of resistance will be a key determinant of which agent can be used. The following table illustrating activity of the novel antimicrobials is useful aid in deciding on management options:The diagram illustrating activity of the novel antimicrobials is useful aid in deciding on management options:AmpC, ampicillin C β-lactamase enzyme; EMA, European Medicines Agency; ESBL, extended spectrum β-lactamase; IMP, active-on-imipenem; KPC, *K. pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase-48; VIM, Verona integron-encoded metallo-β-lactamase. There is no comprehensive guidance on this subject. The closest example of current UK guidance for CPE/CRE is that published by the UKCPA4 in 2020. This guidance does not cover Acinetobacter or difficult to treat pseudomonas.**Suspected resistant pathogen infection:** Choice of antibacterial(s) at this stage must be considered based on microbiological factors relating to the patient (e.g. previously isolated resistant organism) or the environment (local epidemiology of bacterial resistance mechanisms). There is no guidance that exists to support this decision and treatment will be decided by the attending microbiologist. The choice of management again may be aided through knowledge of the relevant activity of the antibacterial.References:1.Electronic Medicines Compendium. Zavicefta 2 g/0.5g powder for concentrate for solution for infusion. Accessed 11/2020, 2020.<https://www.medicines.org.uk/emc/medicine/33061>2.Tamma PD, Hsu AJ. Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms. *Journal of the Pediatric Infectious Diseases Society*. 2019;8(3):251-260. Journal of the Pediatric Infectious Diseases Society 3.Electronic Medicines Compendium. Vaborem 1 g/1 g powder for concentrate for solution for infusion. Accessed 11/2020, 2020. [www.medicines.org.uk/emc/product/10813](http://www.medicines.org.uk/emc/product/10813%20) 4.<https://academic-oup-com.eu1.proxy.openathens.net/jacamr/article/2/3/dlaa075/5917871> | Thank you for your comments and references. No action required |
| Pfizer Ltd  | **Question 3)**The chief determinant for effective treatment in resistant infection treatment is mechanism of resistance and antibacterial sensitivity. UKCPA1 and IDSA2 guidance are the two most relevant documents on this subject are chiefly pathogen oriented. Therefore, we consider pathogen directed management the most paramount. Although pathogen type/resistance mechanism is the main determinant for treatment selection there are also examples where infection site influences treatment selection: e.g. - Aminoglycosides and colistin are less appropriate agents for ventilator associated pneumonia3 - Tigecycline is only licensed for management of cIAI and cSSTI4References:1.https://academic-oup-com.eu1.proxy.openathens.net/jacamr/article/2/3/dlaa075/5917871 2.IDSA 3. www.medscape.com/answers/234753-38467/what-is-the-role-of-aminoglycosides-in-the-treatment-of-ventilator-associated-pneumonia-vap , 4. <https://www.medicines.org.uk/emc/medicine/17779/> | Thank you for your comments and references. No action required. |
| Pfizer Ltd | **Question 4)**Pfizer’s view is that the criteria outlined to identify the primary indication should also include Real-World Evidence where plausible. In addition, the criteria used to identify the primary indication should be dependent on the antibiotic and the proposed positioning or value it offers to society. Therefore, all criteria should be used as part of the assessment with consideration taken as to which is the most relevant for the antibiotic in question.An approach to modelling multiple indications and pathogen combinations which includes several considerations to EEPRU’s value framework through a dynamic disease transmission model has been demonstrated through publications1, thereby demonstrating its plausibility. Sequentially, a more pragmatic approach to other indications can be taken where there is less available data, whereby Pfizer would like to see a large emphasis on the mitigation of uncertainty through expert elicitation and a practical yet novel approach to the revising of value based on gaps in data for modelling.References:1.Gordon J, Darlington O, McEwan P, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38(8):857-869. doi:10.1007/s40273-020-00906-6 | Thank you for your comments and reference. No action required. |
| Pfizer Ltd  | **Question 5)**Pathogen directed modelling is likely to generate the greatest value modelling. In the case where options are limited comparators may include options illustrated in table 1. Colistin, temocillin, fosfomycin and aminoglycosides are among the other potential options here. | Thank you for your comments. No action required |
| Pfizer Ltd | **Question 6)**In considering pathogen diagnostics for Gram negative aerobic infection it is necessary to consider broadly the types of infection relevant to Cedfiderocol; namely, P. aeruginosa, ESBL and carbapenem resistant Enterobacterales (CRE/CPE). Technologies employed will differ according to the trust and the suspected pathogen and suspected site of infection.***Pathogen diagnosis for incident infection***Patients that present a fever or have fever during a hospital inpatient stay should have blood and suspected infection site sampling to detect appropriate organisms. The process of full culture and sensitivity may take 48-72 hours in such cases and includes the use of automated and manual AST methods. The particular technology employed locally is trust dependent.A full sensitivity analysis or molecular diagnostic may be required, and smaller trusts will need to send the sample to the PHE Bacteriology reference department (BRD) to complete this. This can be associated with quite a significant delay to full identification of the pathogen(s) and their resistance mechanism.***Pathogen diagnosis for suspected CPE/CRE infection***PHE have outlined a framework for detection and containment of CPE. A newly awaited resource for is underway which underwent consultation in 2020.1: At the essence of this guidance is CRE/CPE risk factor scoring for all emergency and elective patient admissions who may or may not present with signs of infection. The guidance recognises that there is evidence to support CPE colonisation precedes invasive infection, therefore when risk factors are detected, targeted rectal screening for CRE/CPE is undertaken. All patients in augmented care or high-risk units should also be screened as a routine measure. The following patients should be strongly considered for screening on admission if they are likely to stay in hospital overnight:* If, in the last 12 months:
	+ been previously identified as CPE positive
	+ been an inpatient in any hospital, both in the UK or abroad
	+ had multiple hospital treatments e.g. are dialysis dependant or have had cancer chemotherapy
	+ had known epidemiological link to a known carrier of CPE (includes household and care home contacts of known cases)
* Patients admitted into augmented care or high-risk units
* Other risk factors associated with increased risk and should be considered for screening are:
	+ Patients with immunosuppression
	+ Patients with exposure to broad-spectrum antibiotic courses (such as cephalosporins, glycopeptides, and piperacillin/tazobactam) and in particular carbapenems within the past one month, not covered in other risk groups e.g. those receiving OPAT
	+ Patients admitted from Long Term Care Facilities where higher levels of interventional care are provided e.g. long-term ventilation

Furthermore Boyd et al.2 have also validated a bedside scoring criterion for patients in UK critical care environments to allow for identification and appropriate therapy as early as possible. This result can be obtained within hours and is available to all trusts. If detected and there are signs of infection it would be prudent to cover for resistant infection until full results are obtained. When CPE/CRE is detected through rectal screening, molecular characterisation of the resistance mechanism is undertaken either locally if resources allow or if not are sent to the PHE BRD as above with inherent associated delay.References:1.https://assets.publishing.service.gov.uk/government/uploads/ system/uploads/attachment\_data/file/9265363/Framework\_ of\_actions\_to\_contain\_CPE-draft.pdf2.http://www.sciencedirect.com/science/article/pii/S2213716520301855 | Thank you for your comments and references. No action required. |
| Pfizer Ltd  | **Question 7)**Answered in above response under Equality section. | Comment noted. No action required. |
| Pfizer Ltd | **Question 8)**This has been outlined in the response to question 6. Again, we re-emphasise the importance of PHE risk scoring to fully define the eligible population.  | Comment noted. No action required. |
| Pfizer Ltd  | **Question 9)**Answered in above response under Equality section. | Comment noted. No action required. |
| Pfizer Ltd  | **Question 10)**Pfizer expect the project to deal with current barriers to adoption and the project should be modified based on learnings / outcomes. However, the variability in diagnostics across the UK will continue to present a barrier based on current practice.  | Thank you for your comment. No action required. |

## Section: Additional comments on the draft scope

| Consultee/ Commentator | Comments [sic] | **Action** |
| --- | --- | --- |
| Shionogi | Shionogi looks forward to working with NICE and EEPRU, on this important, unique and challenging assessment project. Given the complexities that have already been described and the likelihood that further assessment challenges will arise, plus the limited time allocated to this scoping process, we suggest that further engagement between NICE/EEPRU and the two manufacturers would be beneficial. This could be both before and after the final Scope is determined, since certain important components of the Scope (most notably the ‘primary indication’ population/s that are selected) remain unresolved. We strongly suggest that further discussions - akin to the Decision Problem Meeting, and Technical Engagement Step – would enable the range of assessments identified by scoping be undertaken in a comprehensive and efficient manner. This would help NICE achieve its overall policy objectives for the assessment project. | Comment noted. NICE and EEPRU will be holding decision problem meetings with the companies after the invitation to participate has been sent. No further action required. |
| Shionogi | References:Hawkey PM, Warren RE, Livermore DM et al. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. J Antimicrob Chemother 2018; 73 Suppl 3: iii2–78.Hughes S, et al. Treating infections caused by carbapenemase-producing Enterobacterales (CPE): a pragmatic approach to antimicrobial stewardship on behalf of the UKCPA Pharmacy Infection Network (PIN) J Antimicrob Chemother 2020 doi:10.1093/jacamr/dlaa075.Ito A, In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. Antimicrobial Agents and Chemotherapy 2018; 62: 1 e01454-17Thalhammer, F., Infektiologie & gastroenterologie Hepatologie 2018:1.Tamma PD, and Hsu AJ, Defining the Role of Novel β-Lactam Agents That TargetCarbapenem-Resistant Gram-Negative Organisms. J Pediatric Infectious Diseases Society 2019; 8: 251–60.Yamano Y, In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria Clinical Infectious Diseases 2019; 69: S544–51. Longshaw C, et al. In vitro activity of the siderophore cephalosporin, cefiderocol, against molecularly characterized, carbapenem-non-susceptible Gram-negative bacteria from Europe. JAC Antimicrob Resist 2020 doi:10.1093/jacamr/dlaa060. | Comment noted. Thank you for the references. NICE, EEPRU and the committee will be considering all relevant information during the evaluation. No action required |
| British Thoracic Society | CF patient with more advanced disease, and lower lung function may require treatment for infections caused by aerobic gram‑negative organisms with limited treatment options. This new Antibiotic is welcomed in this context and would only apply to as small number of patients.  | Comment noted. No action required. |
| British Society for Antimicrobial Chemotherapy | No comment  | Comment noted. No action required. |
| NHS England & NHS Improvement | The scope won’t include defined place in therapy for these two products and NHSE&I expects that place in therapy and conditions for use (e.g., micro approval only) will continue to be for local determination. | Comment noted. No action required. |
| Scottish Government/Scottish Antimicrobial Prescribing Group/Scottish Medicines Consortium | No comment | Comment noted. No action required. |
| MSD | No comment | Comment noted. No action required. |
| Public Health Wales  | No comment | Comment noted. No action required. |
| Pfizer Ltd | No comment  | Comment noted. No action required. |

**The Royal College of Physicians would like to endorse the response submitted by the British Thoracic Society.**