Professional and NHS organisation submission template

Cefiderocol for treating severe aerobic Gram-negative bacterial infections

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| Thank you for agreeing to give us your organisation’s views on this technology and its possible use in the NHS.  You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.  To help you give your views, please use this questionnaire. **You do not have to answer every question** – they are prompts to guide you. The text boxes will expand as you type.  **Information on completing this submission**   * Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable * We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. * Your response should not be longer than 13 pages. |

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| **About you** |  |
| 1. Your name | xxxxxxxxxxxxxx |
| 2. Name of organisation | Intensive Care Society |
| 3. Job title or position | xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx |
| 4. Are you (please tick all that apply): | an employee or representative of a healthcare professional organisation that represents clinicians?  a specialist in the treatment of people with this condition?  a specialist in the clinical evidence base for this condition or technology (for example, an investigator in clinical trials for the technology)?  commissioning services for a CCG or NHS England in general?  commissioning services for the condition for which NICE is considering this technology?  responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?  other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | The Intensive Care Society (ICS) is a charity with 50 years of accumulated experience in delivering education, training, and leading research into intensive care. We do this so that intensive care staff are supported emotionally and intellectually. We know that they learn from each other in both formal and informal professional networking environments. Our experience tells us that informal networks allow tacit knowledge exchange and learning to take place. It makes it more likely that one professional will pick up the phone and ask for help from another. This is positive for their mental health and patient care. We provide the networking environment, educational content, and informal peer support for intensive care workers to learn, develop, research and lead. We provide networks, systems, and support for them to care for intensive care patients as well as the relatives and friends of those patients.The ICS is funded by its charitable activities and donations (for full details, see our Trustees Annual Report - [About us | Annual reports & finances (ics.ac.uk)](https://ics.ac.uk/ICS/ICS/Annual-Reports-Finances.aspx)). |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the stakeholder list.]  If so, please state the name of manufacturer, amount, and purpose of funding. | The ICS has not received funding from Pfizer or Shionogi in the last 12 months |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | No |
| **Current treatment of severe gram-negative infections, where resistance is suspected/confirmed** |  |
| 6. What is the main aim of treatment? | On an individual patient level, where that patient requires advanced organ support, eradication and treatment of severe multi-resistant gram negative infections / sepsis and preservation of life.  On a population level, we seek to treat patients with advanced stages of organ failure and altered or deranged physiology requiring supportive therapy. Where these states occur as a result of an infective process, we seek to use of appropriate antimicrobials according to sensitivities where possible to effectively eradicate infection whilst minimising the rates of antimicrobial resistance and transmission of infection. |
| 7. What do you consider a clinically significant treatment response? | 1. Eradication of infection 2. **Resolution of sepsis and advanced states of organ failure** 3. **Transition to a state of remission in patients who are unlikely to achieve full eradication** |
| 8. In your view, is there an unmet need for patients and healthcare professionals? | Due to the increasing global burden of antimicrobial resistance, there is an unmet need both for patients and for clinicians.  Long term infections with multiply resistant organisms such as cUTI result in protracted morbidity, often requiring frequent hospital admissions, often with blood stream infections. The disseminated nature of blood stream infections has a high probability of shock and resultant end organ dysfunction. A combination of these factors, prolonged and repeated courses of anti-microbial agents in this group of patients often leads to selection of resistant organisms. Appropriate microbiology-directed treatment in this patient group will reduce the likelihood of requiring intensive care services.  In the risk based scenario of severe hospital acquired pneumonia or ventilator associated pneumonia, prompt treatment in patients with a perceived risk of infection with carbapanemase-producing enterbacterales is likely to reduce the requirement for ongoing multi-organ support and may positively impact the duration of mechanical ventilation. Prompt treatment with appropriate antimicrobials may also reduce transmission rates. Identification of susceptibility will enable a focused review of antimicrobial spectrum and appropriate de-escalation too will reduce the potential for resistance. |
| 9. How is the condition currently treated in the NHS? |  |
| * Are any clinical guidelines used in the treatment of the condition, and if so, which? | <https://uroweb.org/wp-content/uploads/18_Urological-infections_LR.pdf>  (From 2013) |
| * Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | Pathways of care will be mostly defined on a local level and depend on patient population demographic variation and also centre type, where specialist centres are likely to see a higher number of specialist referrals, and are likely to be treating patients that are immunosuppressed and or transplant recipients. Patients presenting with cUTI are a heterogeneous population and management will cover the spectrum of outpatient management all the way through to intensive care management. MDR pneumonia in ventilated patients is often associated with poor empiric selection of antimicrobials, increased morbidity, mortality, prolonged mechanical ventilation and duration of intensive care. Inclusion criteria to treat patients with potential CPE VAP will require careful consideration (see q 14 below).  **It is worth noting that the pathway of care for this proposed commissioning / funding model will require extensive consideration for patients that fit inclusion criteria in terms of application, prescribing, dispensing/supply and audit trail. I suggest learning from the model used for the roll out of tocilizumab in treatment of COVID-19 in the application of Blueteq to support compliance (with HVCS and PICOs) and audit.** |
| * What impact would the technology have on the current pathway of care? | Potential definitive therapy with cefiderocol is likely to reduce hospital readmissions and also may lead to an earlier successful treatment in patients requiring intensive care services. This is also likely to result in a positive impact on quality of life outcomes. Success of this funding / procurement model is likely to have significant benefits for the UK health sector in negotiating acquisition costs based on perceived or (in the future) actual benefit across the health system. |
| **The use of the technology** |  |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | Cefiderocol is already in use in the NHS and is recommended in the following guidelines:  [**https://academic.oup.com/jacamr/article/2/3/dlaa075/5917871**](https://academic.oup.com/jacamr/article/2/3/dlaa075/5917871)  However it is noted that in the [CREDIBLE-CR study](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30796-9/fulltext) there was a numerically higher all cause mortality in patients treated with cefiderocol (where 80% of the total population received cefiderocol as monotherapy) when compared with best available therapy (BAT). Microbiological cure rates were similar, also when compared to BAT. I would therefore support the recommendation of [Hughes, Gilchrist, Hear et al](https://academic.oup.com/jacamr/article/2/3/dlaa075/5917871) that cefiderocol may, in the context of empiric therapy, be used in combination with other antimicrobial agents (perhaps to be decided at an individual trust level). |
| * To what extent and in which population(s) is the technology being used in your local health economy? | **The ICS does not currently have any specific recommendations on the treatment of either of the two HVCSs of PICOs.** |
| * How does healthcare resource use differ between the technology and current care? | The significant difference here is that of the funding model. Also, where cefiderocol is used to treat patients with potential CPE VAP, appropriate PCR testing will allow rapid de-escalation, focusing therapy or addition of appropriate sensitivity based additional therapy, minimising resistance selection pressure, optimising cure rate. This will optimise appropriate use and maximise value, however centres that do not have immediate access to PCR tests may be slower to deescalate or optimise therapy and appear to be higher per patient consumers. Bearing in mind the additional mortality in [CREDIBLE-CR study](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30796-9/fulltext), optimisation of adjunctive/additional antimicrobials, and any further mortality based studies, early optimisation of therapy / combination will be of high importance. There may also be (although not proven) a greater risk of selection of resistant organisms where de-escalation may be suboptimal. This will need to be addressed to create a level playing field. |
| * What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) |  |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Data are lacking however this TA will facilitate high quality clinical and quality of life outcome data on the implementation of cefiderocol in the treatment of HVCSs and PICOs.  <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850032/> |
| * Do you expect the technology to increase length of life more than current care? | Yes, microbiological cure rates are similar to standard care and although data are lacking and suggest that optimisation of therapy or addition of appropriate combination therapy especially for patients infected with Acinetobacter spp. this agent significantly broadens the spectrum of available antimicrobials to treat CRE reducing selection pressure and potentially positively influencing resistance patterns for agents in routine practice. Further to this [Choby J., Ozturk T., Satola S., et al](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00194-8/fulltext) made the observation that a larger proportion of Acinetobacter spp. may exhibit heteroresistance increasing the importance of appropriately selecting combinations of therapy. |
| * Do you expect the technology to increase health-related quality of life more than current care? | Yes, see above |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | Patients identified through the HVCS and PICOs represent a significant body of affected patients both at high risk and with known CRE infections. Considering the significantly limited data on implementation of these antimicrobials and the limited data on the commissioning/funding model, the options outlined by EEPRU are reasonable. It may be worth adding caveats for initiating treatment at risk whereby decisions can be taken on a trust level with retrospective applications for funding made to NHSE based on clinical/sensitivity data.  **I remain concerned that there are limited data that address appropriately the observations of an increased all cause mortality with cefiderocol and suggest that where cefiderocol is indicated, an additional antimicrobial based either on sensitivities or most likely pathogen where used in a risk based empiric treatment scenario, be added to therapy, especially where Acinetobacter is isolated or suspected.** |
| 13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | **No** |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | **Yes, inclusion criteria will be required for both HVCSs and PICOs. Inclusion criteria may need to be dynamic in the context of identification of individual trusts / units where an ‘outbreak’ may have been identified.**  **For cUIT, suggested inclusion criteria should include patients with previous CRE infection or colonisation with serine carbapenemase-producing Enterobacterales either through susceptibility testing or PCR.**  **For HAP/VAP in the risk based PICO, some suggested inclusion criteria are as follows, agreement to treat with cefiderocol should be agreed by a consultant in critical care medicine and a consultant microbiologist and include patients that are being or have been treated at a trust / unit that carries a greater risk of CRE infection, patients previously colonised or in close contact with somebody known to be colonised with CRE. In the absence of previous positive microbiology, where PCR facilities allow rapid identification, cefiderocol (plus additional agent with proven or suspected sensitivity dependent on availability of sensitivities) could also be used where empiric carbapenem therapy may have failed. Appropriate and prompt de-escalation is also key for long term (population based) treatment success. PCR identification should be suggested as this will allow rapid identification of pathogen and resistance mechanism and subsequent focusing of therapy (which may include de-escalation of cefiderocol where appropriate). Rapid de-escalation will also reduce likelihood of selection of resistant pathogens.** |
| 15. What is the outcome of any evaluations or audits of the use of the technology? |  |
| **Sources of evidence** |  |
| 16. Do the clinical trials on the technology reflect current UK clinical practice? | This is an area where the evidence base is still emerging and an outcome of the TA is to produce quality patient centred and clinical outcomes based data. |
| * If not, how could the results be extrapolated to the UK setting? |  |
| * What, in your view, are the most important outcomes, and were they measured in the trials? |  |
| * If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? |  |
| * Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? |  |
| 17. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? |  |
| 18. How do data on real-world experience compare with the trial data? |  |
| **Equality** |  |
| 19. Are there any potential [equality issues](https://www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme) that should be taken into account when considering this treatment? | Access to PCR identification, sensitivity and resistance technologies will significantly reduce the time to de-escalation (unpublished data). |
| 20. Consider whether these issues are different from issues with current care and why. |  |
| **Key messages** |  |
| 21. In up to 5 bullet points, please summarise the key messages of your submission. | * Prompt, definitive (antimicrobial) therapy for patients identified to have CRE infections and those in the highest risk categories is likely to improve mortality and quality of life * De-escalation of therapy as directed by PCR testing will be vital to limit selection of resistant bacteria * Auditing inclusion criteria and compliance with identified HVCS and PICOs will be vital to inform to success of a new commissioning/funding model * Treating with definitive (antimicrobial) therapy may reduce selection of resistant strains for other antimocrobials |

Thank you for your time.

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