Evaluation criteria and evidence requirements

# Introduction

Companies that meet the eligibility criteria for the Antimicrobial Products Subscription Model will be invited to submit evidence to demonstrate how their product satisfies the evaluation criteria and evidence requirements set out in this document. A UK panel of experts, convened by NICE to provide recommendations to the Authority (NHS England) and other UK contracting authorities, will meet in private to assess the documentation provided by the company and assign points for each criterion. The product’s score will determine the value band of the contract offered by the authority(ies) to the company. The evaluation panel can recommend 1 of 4 possible contract ‘value bands’ (Table 1), or can recommend no contract if the product scores insufficient points. The score given will depend on the evaluation panel’s view of the strength, quality and relevance of the evidence provided by the company.

**Table 1. Value bands, linked to the evaluation criteria scoring system**

|  |  |  |  |
| --- | --- | --- | --- |
| **Band 1****£20mn per year*****Breakthrough antimicrobial*** | **Band 2****£15mn per year*****Critical new antimicrobial*** | **Band 3****£10mn per year*****Priority new antimicrobial*** | **Band 4****£5mn per year** ***Important new antimicrobial*** |
| Achieves ≥80% of maximum score against evaluation criteria | Achieves 70–79% of maximum score against evaluation criteria | Achieves 60–69% of maximum score against evaluation criteria | Achieves 50–59% of maximum score against evaluation criteria |
| The value of the bands shown in the table are for England only. Each nation will determine the values that will apply for their health system. |

This document provides the following information:

* An overview of the evaluation criteria and scoring system, and how they were developed.
* A description of how the scoring system works, including a hypothetical example.
* A full description of each evaluation criterion and the associated evidence requirements.

# Overview of the evaluation criteria and scoring system

The evaluation criteria were developed by the National Institute for Health and Care Excellence (NICE) and NHS England (NHSE) in consultation with clinical experts from the NHSE Antimicrobial Resistance (AMR) Programme, and have been validated by clinical experts from the UK Government’s Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI).

There are 17 criteria, grouped into 3 categories: ‘relative effectiveness and unmet clinical need’, ‘pharmacological benefit’ and ‘health system benefit’ (Figure 1). Each criterion has a maximum score of 100 points.

Each antimicrobial will receive a total score between 0 and 100. This is a weighted average of the scores that it receives for each of the 17 criteria. The weight assigned to each criterion reflects its relative importance to the overall value of an antimicrobial. In other words, the total number of points available across all criteria is not a simple average or sum of the points scored for each of the 17 criteria.

The weights for the criteria were obtained from an elicitation exercise using the ‘swing weighting’ method, using a sample of clinical experts from the NHSE AMR Programme and the APRHAI Advisory Committee. The most valuable category is ‘relative effectiveness and unmet clinical need’, which is allocated 45% of the overall value, followed by ‘health system benefit’ with 30% and ‘pharmacological benefit’ with 25% of the overall value. ‘Activity against WHO bacterial priority pathogens’ is the most valuable criterion out of the 17, accounting for 12.2% of the overall product value (Figure 1).

**Figure 1: Evaluation criteria and weights within the scoring system**

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The criteria are designed to reflect the broad range of benefits that an antimicrobial could offer patients and health systems in the UK and globally. They were informed by the eligibility criteria used to select the 2 antimicrobials assessed as part of the [pilot project](https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials) to test a new evaluation and payment model, and by the drivers of value identified through the quantitative health economic analyses and committee deliberations conducted as part of the pilot. The evaluation criteria ensure that the following attributes of value are captured (collectively abbreviated to ‘STEDI’ values):

* reducing problems associated with broad-spectrum antimicrobials that cause collateral damage to the microbiota (‘spectrum value’)
* reducing the spread of infection to other people (‘transmission value’)
* ensuring that chemotherapy, surgery and other medical procedures can go ahead (‘enablement value’)
* providing a range of treatment options to reduce the risk of resistance developing (‘diversity value’)
* preparing for existing antimicrobials becoming ineffective (‘insurance value’).

By rewarding antimicrobials that target the most threatening pathogens and resistance mechanisms (criteria 1A and 1B), the criteria capture insurance and enablement value by awarding more points to products that help to guard against potential future scenarios with no effective available treatment options for those with resistant infections (and thereby enabling high-risk procedures that may have otherwise been cancelled). The criteria also value treatments that have minimal impacts on the gut microbiome (spectrum value; criterion 2F) and achieve rapid microbiological eradication to reduce transmission risks to others (criterion 1D). Treatments that reduce hospital-led care and offer other health system benefits could also be expected to enable health service provision and reduce transmission (criteria 3A to 3G). Lastly, the criteria also reward products that increase the diversity of treatments available. A new product within an antimicrobial class that overcomes the key resistance mechanisms associated with that class is rewarded in criterion 1B, and 1C is aimed at incentivising development of treatments in areas with fewer or lower quality treatment options.

# How each antimicrobial will be scored

An overall product score is calculated by multiplying each criterion score (between 0 and 100) by the criterion weight (between 0 and 1) and summing across all of the criteria. The example in Figure 2 illustrates how a score would be calculated for a hypothetical product. For this product the evaluation panel have concluded that the product is highly novel and successfully addresses high global and UK unmet needs. This yields an overall score of 80/100 and would be recommended for the highest contract value band of £20 million per year.

**Figure 2: Hypothetical product profile illustrating the scoring system**

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Scoring rules differ across the criteria. For the following 4 criteria, the score is derived additively with the possibility of products attaining multiple criterion levels:

* Activity against WHO bacterial priority pathogens (1A)
* Activity against resistance mechanisms (1B)
* Drug exposure at the site of infection (2C)
* Impact on the gut microbiome (2F).

For the remaining 13 criteria, products are allocated to the highest level justified by the submitted evidence. The scoring for each criterion is described in full in the section ‘Evaluation criteria and evidence requirements’.

# Evaluation criteria and evidence requirements

This section provides a full description of each evaluation criterion, including the points available and the types of evidence that companies are required to submit for consideration by the evaluation panel. This includes admissible study designs and, where relevant, evidence hierarchies, methodological standards, and guidance on minimum sample sizes.

When assigning points, the evaluation panel will assess and consider the strength, quality and relevance of the submitted evidence. For example, if the panel members conclude that a study is of low methodological quality or not relevant to the evaluation, they may exclude that study from consideration when assigning points.

Several criteria require companies to submit evidence compared with current best standard care in the UK, which may differ across different indications. Best standard care will not be defined in the scope for the evaluation; the scope will focus on the population (including the pathogens, resistance mechanisms and infection sites). Companies should include in their submission an explanation of UK best standard care for the population(s) under evaluation, and submit the relevant evidence.

A number of criteria refer to a “reference marketing authorisation”. This is a marketing authorisation in force, or expected to be in force by 31st July 2025, in respect of a product, allowing it to be lawfully placed on the market in Great Britain. The therapeutic indications for the product will be determined by reference to the Summary of Product Characteristics (SmPC) accompanying that authorisation.

The following documents must be submitted at the same time as the evidence submission:

* Full journal articles for all publications that are cited in the evidence submission. The company must have copyright clearance for these articles. References must also be provided as a separate RIS file.
* Clinical trial reports and protocols for all clinical studies cited in the evidence submission.
* Marketing authorisation documentation:
	+ a draft or final Summary of Product Characteristics (SmPC) for the reference marketing authorisation, and
	+ a draft or final European public assessment report (EPAR).

If the SmPC for the reference marketing authorisation and/or EPAR is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered and should be submitted.

Companies must include a full and comprehensive description of the evidence for the antimicrobial specific to each criterion within the submission template, for consideration by the panel. Journal articles and other listed documents are requested to enable the panel to quality assure the evidence submission. The evidence submission must not include embedded documents or URL links.

For criteria 1B (‘Activity against resistance mechanisms’) and 2D (‘Absence of cross resistance’), companies are required to provide evidence generated by the UK Health Security Agency (UKHSA). Where a company has initiated the process with UKHSA but is unable to submit evidence by the stated deadline because the UKHSA testing process has not been completed, then:

* The company will inform the Authority (NHS England) that the deadline cannot be made, provide a date by which the evidence will be submitted and make best endeavours to submit the evidence by the new agreed deadline.
* The Authority (NHS England) will inform NICE of the new deadline.
* Where the new deadline is before the scheduled date of the evaluation panel meeting for the product, NICE will endeavour to use the evidence submitted by the company.
* Where the evidence is not submitted by the company in time for inclusion at the evaluation panel meeting, the panel will sit as planned and use a default interim score of 50 for the product on criteria 1B and 2D.
* Once evidence has been submitted by the company, NICE will endeavour to complete the evaluation using the evidence.
* If at the point of the Authority (NHS England) being ready to make a contract award offer, the evidence has still not been submitted, at the discretion of the Authority (NHS England), the Authority (NHS England) may decide to either:
	+ offer a contract award based on the evaluation of the panel using the available evidence, or
	+ defer a contract award offer until the evidence has been submitted.

Where a contract award offer is made with incomplete evidence and that award is accepted by the company, by accepting the contract the company is also accepting any changes to the contract terms and value that may result once the UKHSA evidence is submitted and the evaluation of criteria 1B and 2D is completed.

For the avoidance of doubt, this provision about incomplete evidence only applies to criteria 1B and 2D, and for evidence that is generated by UKHSA.

# Category 1: Relative effectiveness and unmet clinical need

# Criterion 1A: Activity against WHO bacterial priority pathogens

List the pathogens from the [WHO bacterial priority pathogens list (2024)](https://www.who.int/publications/i/item/9789240093461) against which the antimicrobial is active, with supporting evidence.

Points for this criterion are additive. Antimicrobials will be allocated a score for this criterion based on the top 3 highest scoring pathogens it is active against (table 2). A maximum score of 100 is awarded to any antimicrobial that is active against all 3 of the WHO ‘critical priority’ pathogens.

A product will receive points only for indications that are covered by its reference marketing authorisation, or the marketing authorisation that is expected within the cut-off date stipulated by the eligibility criteria for the procurement process.

**Table 2. Points available for criterion 1A**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Enterobacterales, carbapenem-resistant [WHO critical priority] | **36** |
| 2 | Enterobacterales, third-generation cephalosporin-resistant [WHO critical priority] | **35** |
| 3 | Acinetobacter baumannii, carbapenem-resistant [WHO critical priority] | **29** |
| 4 | Salmonella Typhi, fluoroquinolone-resistant [WHO high priority] | **27** |
| 5 | Shigella spp., fluoroquinolone-resistant [WHO high priority] | **27** |
| 6 | Enterococcus faecium, vancomycin-resistant [WHO high priority] | **27** |
| 7 | Pseudomonas aeruginosa, carbapenem-resistant [WHO high priority] | **27** |
| 8 | Non-typhoidal Salmonella, fluoroquinolone-resistant [WHO high priority] | **24** |
| 9 | Neisseria gonorrhoeae, third-generation cephalosporin, and/or fluoroquinolone-resistant [WHO high priority] | **24** |
| 10 | Staphylococcus aureus, methicillin-resistant [WHO high priority] | **22** |
| 11 | Group A Streptococci, macrolide-resistant [WHO medium priority] | **15** |
| 12 | Streptococcus pneumoniae, macrolide-resistant [WHO medium priority] | **15** |
| 13 | Haemophilus influenzae, ampicillin-resistant [WHO medium priority] | **11** |
| 14 | Group B Streptococci, penicillin-resistant [WHO medium priority] | **11** |

# Guidance on evidence requirements

Information about the antimicrobial’s activity against pathogens on the WHO bacterial priority pathogens list should be extracted from the Summary of Product Characteristics (SmPC) accompanying the reference marketing authorisation (under Section 5.1 ‘Pharmacodynamic properties’) and European public assessment report (EPAR), if available at the time of the evaluation, and included in the company submission. A draft SmPC and draft EPAR will be accepted. If the SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

In addition to the SmPC and EPAR, companies should submit the results of in vitro susceptibility testing to confirm the resistance profile of the pathogens. Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series)

Laboratory methods and breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are preferred. If studies using EUCAST methods and breakpoints are not available, those set by the Clinical and Laboratory Standards Institute (CLSI) will then be accepted. Both UK and international surveillance data on susceptibility will be accepted for this criterion. Submissions should specify the approach to quality assurance that was adopted during the development of the evidence and quality standards applied, such as those stipulated by the [Royal College of Pathologists](https://www.rcpath.org/profession/publications/standards-for-microbiology-investigations.html).

# Criterion 1B: Activity against resistance mechanisms

Describe the activity of the product against the key determinants of antimicrobial resistance in table 3, and provide supporting evidence.

Points for this criterion are additive, and are separated into 2 sections, as shown in table 3.

An antimicrobial can achieve all of the levels in Section 1 if it is active against the top 3 mechanisms of carbapenem resistance:

* at least one of the UK-relevant metallo β-lactamases (MBLs) and
* at least one of the UK-relevant non-MBL serine carbapenemases and
* at least one of the UK-relevant non-enzymatic causes of multi-drug resistance in carbapenem-resistant organisms.

An antimicrobial can achieve a maximum of 1 level of Section 2 if it is active against at least one of the UK-relevant resistance mechanisms of its respective antimicrobial class.

The maximum score of 100 can be achieved by:

* Section 1: activity against all 3 of the mechanisms of carbapenem resistance (30 + 25 + 25 = 80 points) and
* Section 2: a beta lactam agent that is active against other UK-relevant beta-lactam resistance mechanisms (20 points).

For non-beta lactam agents, a maximum of 15 points is available from Section 2, giving a maximum possible score of 95.

An antimicrobial of a new class will automatically achieve a score of 20 in Section 2, plus the score achieved from activity against each of the 3 mechanisms of carbapenem resistance listed in Section 1.

The evaluation panel will assign points based on their assessment of a product’s in vitro activity against a range of UK-relevant pathogens with known resistance mechanisms to carbapenems (Ambler subclasses). The UK-relevant Ambler subclasses will be specified by UKHSA as part of the strain panel testing process described in the ‘guidance on evidence requirements’ below.

A product will receive points only for indications that are covered by its reference marketing authorisation, or the marketing authorisation that is expected within the cut-off date stipulated by the eligibility criteria for the procurement process.

**Table 3. Points available for criterion 1B**

|  |  |
| --- | --- |
| Criterion level | Points |
| **Section 1: Maximum of 3 selections from the following:** |
| 1 | An antimicrobial that is active against one or more of the UK-relevant metallo β-lactamase (MBL) mechanisms of resistance | 30 |
| 2 | An antimicrobial that is active against one or more of the UK-relevant non-MBL serine carbapenemases | 25 |
| 3 | An antimicrobial that is active against UK-relevant carbapenem-resistant pathogens that express non-enzymatic causes of multi-drug resistance (e.g. efflux pumps or porin loss) | 25 |
| **Section 2: Maximum of 1 selection from the following:** |
| 4 | A beta lactam or antimicrobial with the same or related mechanism of action that is active against one or more of the UK-relevant beta-lactam resistance mechanisms  | 20 |
| 5 | An antimicrobial not in the beta lactam class that is active against one or more of the UK-relevant resistance mechanisms associated with its class | 15 |

# Guidance on evidence requirements

Activity is confirmed using in vitro susceptibility evidence. Products should be tested against a panel of UK-relevant pathogens defined by UKHSA, based on clinical need and the spectrum of activity of the antimicrobial. The strain panel will consist of a maximum of 430 clinical bacterial isolates of diverse species and with variable resistance phenotypes/resistance mechanisms that originate from diagnostic laboratories throughout the UK. The panel will indicate whether the product has reduced susceptibility in isolates with the 3 carbapenem-resistance mechanisms included in Section 1 of the criterion and the class-specific resistance mechanisms included in Section 2.

The UKHSA panel testing process is the same as the one described for cross-resistance testing in Criterion 2D, and will produce evidence for both criteria simultaneously.

If testing from UKHSA has not been commissioned, or does not cover the UK-relevant pathogens, zero points will be awarded. If testing has been commissioned to UKHSA but has not been submitted in time to be considered by the evaluation panel, the product will receive a default interim score of 50 points. The company will be required to submit the UKHSA results as soon as they are available, and the product will be considered for re-evaluation to update the score for criterion 1B and overall product score.

# Criterion 1C: Activity against UK unmet needs

Describe how the product addresses UK unmet needs in table 4. This should be based on (i) the activity of the product against the key pathogens that have been identified as high or moderate unmet need and (ii) how the product is effective at treating any of the clinical syndromes relevant to those pathogens, according to the designations in tables 5 and 6. Provide supporting evidence for both of these aspects.

Products not active against pathogens identified as high or moderate unmet need, or that do not have evidence of non-inferior or superior effectiveness compared with current UK best standard care in any of the relevant clinical syndromes will be awarded a score of zero.

A product will receive points only for indications that are covered by its reference marketing authorisation, or the marketing authorisation that is expected within the cut-off date stipulated by the eligibility criteria for the procurement process.

**Table 4. Points available for criterion 1C**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Active against any of the UKHSA high unmet need pathogens (see table 5) with evidence of non-inferior or superior effectiveness compared with current UK best standard care in treating any of the relevant clinical syndromes  | 100 |
| 2 | Active against any of the UKHSA moderate unmet need pathogens (see table 6) with evidence of non-inferior or superior effectiveness compared with current UK best standard care in treating any of the relevant clinical syndromes | 45 |
| 3 | Not active against any of the UKHSA high or moderate unmet need pathogens | 0 |

The designation of pathogens to levels of unmet need (see tables 5 and 6) was developed under UKHSA's guidance and accounted for multiple aspects of unmet need, including the prevalence and severity of infections, availability of well-tolerated and effective treatment options and future outbreak risk. The unmet need levels are defined in terms of the following characteristics, although pathogens do not have to meet every condition to be designated the respective level:

* High unmet need: High to very high prevalence and/or severity of infection, few effective and well-tolerated treatment options available, high population risk associated with future outbreaks
* Moderate unmet need: Moderate to high burden prevalence and/or severity of infection, some effective and well-tolerated treatment options available, moderate population risk associated with future outbreaks
* Low unmet need (no points awarded): Low to moderate prevalence and/or severity of infection, several effective and well-tolerated treatment options available, low population risk associated with future outbreaks

When assessing unmet need, the panel will take into consideration evidence of effectiveness in the clinical syndromes with which the relevant pathogens are most frequently associated.

**Table 5. High unmet need pathogen list**

|  |  |  |
| --- | --- | --- |
| Pathogen | Antibiotic resistance | Relevant clinical syndromes |
| Enterobacterales | Carbapenem-resistant ORThird-generation cephalosporin-resistant | BSI, CNSI, IAI, RTI, SSTI, UTI  |
| Acinetobacter spp.   | Carbapenem-resistant  | BSI, CNSI, RTI, SSTI,  |
| Pseudomonas spp.   | Carbapenem-resistant   | BSI, CNSI, RTI, SSTI, UTI,  |
| Enterococcus spp.   | Glycopeptide-resistant   | BSI, CNSI, IAI, SSTI, UTI,  |
| Neisseria gonorrhoeae | Third-generation cephalosporin-resistant ORFluoroquinolone-resistant  | STI, UTI |
| Shigella spp. | Fluoroquinolone-resistant  | GII, IAI  |
| Mycobacterium tuberculosis | MDR-TB OR XDR-TB | CNSI, IAI, RTI, SSTI  |
| Abbreviations: BSI = Blood stream infection; CNSI = central nervous system infection; GII = gastrointestinal infection; IAI = intra-abdominal infection; MDR = multidrug-resistant; RTI = respiratory tract infection; SSTI = skin and soft tissue infection; STI = sexually transmitted infection; TB = tuberculosis; UTI = urinary tract infection; XDR = extensively drug-resistant  |

**Table 6. Moderate unmet need pathogen list**

|  |  |  |
| --- | --- | --- |
| Pathogen | Antibiotic resistance | Relevant clinical syndromes |
| Enterobacterales | Aminoglycoside-resistant OR Fluoroquinolone-resistant | BSI, CNSI, IAI, RTI, SSTI, UTI,  |
| Acinetobacter spp.   | Aminoglycoside-resistant ANDfluoroquinolone-resistant | BSI, CNSI, RTI, SSTI |
| Pseudomonas spp.   | Resistant to 2 or more antimicrobial groups (excluding resistance to carbapenems)   | BSI, CNSI, RTI, SSTI, UTI |
| Staphylococcus aureus   | Methicillin-resistant   | BSI, CNSI, GII, IAI, RTI, SSTI, UTI,  |
| Helicobacter pylori | Clarithromycin-resistant | GII, IAI  |
| Campylobacter spp. | Fluoroquinolone-resistant  | GII, IAI |
| Salmonella spp. | Fluoroquinolone-resistant  | GII, IAI |
| Abbreviations: BSI = Blood stream infection; CNSI = central nervous system infection; GII = gastrointestinal infection; IAI = intra-abdominal infection; RTI = respiratory tract infection; SSTI = skin and soft tissue infection; STI = sexually transmitted infection; UTI = urinary tract infection |

# Guidance on evidence requirements

Information about the antimicrobial’s activity against specific multidrug-resistant pathogens should be extracted from the Summary of Product Characteristics (SmPC) for the reference marketing authorisation (under Section 5.1 ‘Pharmacodynamic properties’) and European public assessment report (EPAR), if available at the time of the evaluation, and included in the company submission. A draft SmPC and draft EPAR will be accepted. If the SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

In addition to the SmPC and EPAR, companies should submit the results of in vitro susceptibility evidence. Laboratory methods and breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are preferred. If studies using EUCAST methods and breakpoints are not available, those set by the Clinical and Laboratory Standards Institute (CLSI) will then be accepted. Both UK and international surveillance data on susceptibility will be accepted for this criterion. Submissions should specify the approach to quality assurance that was adopted during the development of the evidence and quality standards applied, such as those stipulated by the [Royal College of Pathologists](https://www.rcpath.org/profession/publications/standards-for-microbiology-investigations.html).

Evidence of the effectiveness of an antimicrobial for relevant major clinical syndromes should come from the following sources, ordered from highest to lowest methodological quality:

* clinical trials
* registry data analyses
* observational studies
* case series studies.

These studies should preferably be in the UK population. However, studies in non-UK populations will be considered provided that the comparator used in the trial is current best standard care in the UK. Refer to the [NICE real-world evidence framework](https://www.nice.org.uk/corporate/ecd9/chapter/overview) for guidance on the use of real-world evidence.

Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series) All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](https://www.york.ac.uk/crd/) (University of York Centre for Reviews and Dissemination). Relevant items of the [CONSORT checklist](http://www.consort-statement.org/) should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case.

# Criterion 1D: Clinical effectiveness compared with current UK best standard care

Provide evidence for the clinical effectiveness of the antimicrobial relative to current best standard care in the UK. This includes clinical outcomes only; adverse events are included in criterion 3A.

The maximum number of points available for this criterion is 100. Points will be awarded if the required level evidence is provided for any one of the pathogens or clinical syndromes that the product treats.

A product will receive points only for indications that are covered by its reference marketing authorisation, or the marketing authorisation that is expected within the cut-off date stipulated by the eligibility criteria for the procurement process.

**Table 7. Points available for criterion 1D**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Randomised clinical trial evidence of superiority in any primary clinical outcome (e.g. mortality, clinical cure), compared with current best standard care in the UK | 100 |
| 2 | Both of the following:* Randomised clinical trial evidence of non-inferiority in primary clinical outcomes compared with current best standard care in the UK

**AND** * Randomised clinical trial evidence of superiority in microbiological eradication compared with current best standard care in the UK
 | 65 |
| 3 | Randomised clinical trial evidence of non-inferiority in any primary clinical outcome, compared with current best standard care in the UK | 50 |
| 4 | None of the above | 0 |

# Guidance on evidence requirements

The types of admissible evidence for this criterion are specified within the level descriptions.

It is recognised that, for several reasons, clinical trials for antimicrobials usually include people with infections that are expected to be susceptible to both the new agent and comparator i.e. it is not possible to provide definitive evidence in people for whom the new drug is expected to be used in clinical practice: those with severe, difficult-to-treat infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens. Therefore, clinical evidence for susceptible pathogens will be accepted.

These studies should preferably be in the UK population. However, studies in non-UK populations will be considered provided that the comparator used in the trial is current best standard care in the UK.

Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series) All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](https://www.york.ac.uk/crd/) (University of York Centre for Reviews and Dissemination). Relevant items of the [CONSORT checklist](http://www.consort-statement.org/) should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case.

# Category 2: Pharmacological benefit

# Criterion 2A: Chemical entity novelty

Describe the degree of novelty of the product with respect to chemical class and/or mechanism of action. For products licenced within a combination, this relates to any of the products within the combination.

The evaluation panel will assign points based on information on chemical class and mechanism of action within the [WHO’s ‘Antibacterial agents in clinical and preclinical development’ report (2023)](https://www.who.int/publications/i/item/9789240094000). For products that do not feature in the WHO report, the evaluation panel will assign points based on their own judgement, informed by any relevant information from current and previous WHO reports.

**Table 8. Points available for criterion 2A**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Prototype of new chemical class | 100 |
| 2 | Additional member of new chemical class or novel mechanism of action | 75 |
| 3 | Major adaptation of existing class or mechanism of action | 45 |
| 4 | Existing class of minor adaptation of existing mechanism of action | 0 |

# Guidance on evidence requirements

The novelty of the chemical class of an antimicrobial should be defined in accordance with the [WHO’s ‘Antibacterial agents in clinical and preclinical development’ report (2023)](https://www.who.int/publications/i/item/9789240094000).

Details of the chemical class and mechanism of action should be extracted from the reference marketing authorisation documentation:

* a draft or final Summary of Product Characteristics (SmPC) for the reference marketing authorisation (Section 5.1, ‘Pharmacodynamic properties’, and included in the company submission), and
* a draft or final European public assessment report (EPAR).

Draft documentation will be accepted. If the reference marketing authorisation documentation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

# Criterion 2B: Target site novelty

Confirm whether the antimicrobial acts on a new pathogen-specific target compared with existing agents in use for the relevant pathogen(s). Provide supporting evidence demonstrating that the target site is novel or compromises an existing target site in a novel way.

**Table 9. Points available for criterion 2B**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Novel target site not utilised by any existing antimicrobials | 100 |
| 2 | Existing target site compromised in a different way by the new agent | 80 |
| 3 | None of the above | 0 |

# Guidance on evidence requirements

Target site should be confirmed by studies of the pharmacodynamic profile of the antimicrobial. It can also be confirmed using the [WHO’s ‘Antibacterial agents in clinical and preclinical development’ report (2023)](https://www.who.int/publications/i/item/9789240094000).

Details of the target site should be extracted from the reference marketing authorisation documentation:

* a draft or final Summary of Product Characteristics (SmPC) for the reference marketing authorisation (Section 5.1, ‘Pharmacodynamic properties’, and included in the company submission), and
* a draft or final European public assessment report (EPAR).

Draft documentation will be accepted. If the reference marketing authorisation documentation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

# Criterion 2C: Drug exposure at the site of infection

State whether the antimicrobial achieves clinically relevant drug exposures at the site of infection, and provide supporting evidence.

Points for this criterion are additive. Antimicrobials will be allocated a score for this criterion based on the number of sites with clinically relevant drug exposures. A maximum score of 100 is awarded to an antimicrobial with evidence of clinically relevant drug exposures in the 4 anatomical sites listed in table 10.

**Table 10. Points available for criterion 2C**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Clinically relevant blood drug exposures | 30 |
| 2 | Clinically relevant lung drug exposures  | 30 |
| 3 | Clinically relevant cerebrospinal fluid drug exposures  | 20 |
| 4 | Clinically relevant urine drug exposures | 20 |

# Guidance on evidence requirements

Clinically relevant partitioning to the site of infection should be confirmed by relevant pharmacodynamic, microbiological and pharmacological studies.

The strongest evidence for site-specific activity and demonstration of clinically relevant drug exposures at the site of infection comes from establishing dose‑exposure-response relationships in well characterised models that are faithful mimics of clinical disease. These could include hollow fibre infection models, or other in vitro models and/or laboratory animal models of infection. Ideally, these experimental-to-clinic bridging studies consider and correct for drug exposures at the effect site in the experimental model and humans. Bridging studies are especially relevant for assessing epithelial lining fluid and urine drug exposures for pneumonia and urinary tract infections, respectively. Ideally, 2 endpoints should be considered: (1) drug exposures that result in antimicrobial activity that is relevant for the distribution of minimum inhibitory concentrations (MICs) likely to be encountered in clinical practice; (2) drug exposures that suppress the emergence of resistance.

For other diseases (e.g. bone infection, prostatitis) evidence for partitioning of drug is indirect and comes from multiple sources (see below). Evidence is often qualitative or at best semi-quantitative.

Ideally, the relevant tissue drug exposure (target) should be quantified in terms of the magnitude of the relevant pharmacokinetic-pharmacodynamic (PK-PD) index determined in dose fractionation studies e.g. the ratio of area under the curve to the minimum inhibitory concentration (AUC/MIC), the time above MIC, and the ratio of maximum serum concentration to the minimum inhibitory concentration (Cmax/MIC).

Indirect evidence to demonstrate the clinical relevance of drug exposures may include:

* Tissue homogenates from laboratory animal models
* Radiolabelled studies in animals
* Matrix-assisted laser desorption ionization (MALDI) mass spectrometry imaging
* Microdialysis studies
* Specific clinical studies (Phase I) for epithelial lining fluid, cerebrospinal fluid and urine or embedded Phase II/III sub-studies
* Indirect clinical evidence in disease e.g. specific case studies or case series that suggest activity for a disease at the anatomical site in question.

Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series)

# Criterion 2D: Absence of cross resistance

Describe whether the antimicrobial has any cross resistance with current UK best standard care in same class or subclass, and provide supporting evidence.

For products where UK best standard care does not include antimicrobials in the same class or subclass, points will be awarded as described in table 11 based on cross-resistance with antimicrobials in other classes that are considered best standard care in the UK through discussion with UKHSA (see guidance on evidence requirements).

**Table 11. Points available for criterion 2D**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | No known cross-resistance with best standard care in same class or subclass | 100 |
| 2 | Partial cross-resistance with best standard care in the same class or subclass | 60 |
| 3 | Full cross-resistance with best standard care in same class or subclass  | 0 |

# Guidance on evidence requirements

Cross-resistance should be confirmed via testing at UKHSA laboratories. Chemical class should be defined in accordance with the [WHO’s ‘Antibacterial agents in clinical and preclinical development’ report (2023)](https://www.who.int/publications/i/item/9789240094000). The composition of the panel of antimicrobials to be tested should be agreed through discussion with UKHSA.

Products should be tested against a panel of UK-relevant pathogens defined by UKHSA, based on clinical need and the spectrum of activity of the antimicrobial. The strain panel will consist of a maximum of 430 clinical bacterial isolates of diverse species and with variable resistance phenotypes/resistance mechanisms that originate from diagnostic laboratories throughout the UK. Susceptible isolates will also be included for indication of reduced susceptibility in isolates with resistance mechanisms.

The UKHSA panel testing process is the same as the one described for resistance mechanism testing in Criterion 1B, and will produce evidence for both criteria simultaneously.

If testing from UKHSA has not been commissioned, or does not cover UK-relevant pathogens, zero points will be awarded. If testing has been commissioned to UKHSA but has not been submitted in time to be considered by the evaluation panel, the product will receive a default interim score of 50 points. The company will be required to submit the UKHSA results as soon as they are available, and the product will be considered for re-evaluation to update the score for criterion 2D and overall product score.

# Criterion 2E: Absence of rapidly emerging resistance

Confirm whether the antimicrobial has reduced vulnerability to the emergence of clinically relevant levels of resistant isolates in target pathogens, and provide supporting evidence. 'Clinically relevant’ levels of resistant isolates are defined as levels that would require a change of treatment.

**Table 12. Points available for criterion 2E**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | No known resistant isolates detected at point of assessment in either clinical trials or laboratory | 100 |
| 2 | Clinically relevant levels of resistance detected under laboratory conditions | 75 |
| 3 | Clinically relevant levels of resistance detected from isolates during clinical trials of this product | 25 |
| 4 | Clinically relevant levels of resistance detected from isolates during treatment in clinical trials of other antimicrobials | 0 |

# Guidance on evidence requirements

The types of admissible evidence for this criterion are specified within the level descriptions.

In vitro evidence using laboratory methods and breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are preferred. If studies using EUCAST methods and breakpoints are not available, those set by the Clinical and Laboratory Standards Institute (CLSI) will then be accepted. Submissions should specify the approach to quality assurance that was adopted during the development of the evidence and quality standards applied, such as those stipulated by the [Royal College of Pathologists](https://www.rcpath.org/profession/publications/standards-for-microbiology-investigations/quality-related-guidance.html).

Evidence should be obtained from a systematic review of the literature and should include both UK and international studies. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series) All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](https://www.york.ac.uk/crd/) (University of York Centre for Reviews and Dissemination). Relevant items of the [CONSORT checklist](http://www.consort-statement.org/) should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case.

# Criterion 2F: Impact on gut microbiome

State the impact of the antimicrobial on the gut microbiome, and provide supporting evidence.

Points for this criterion are additive and are separated into 2 sections (table 13). In Section 1 the 2 levels are mutually exclusive alternatives (‘preservation of gut microbiome’ or ‘recovery of gut microbiome’). An antimicrobial can achieve a maximum of 1 level of Section 1 (either 30 points or 60 points) and a maximum of 2 levels of Section 2 (up to 40 points).

‘Clinically relevant’ changes in microbe populations will vary according to the assay used. Typically, ‘no clinically relevant change’ is defined at a threshold of less than 2 log10 fold change in microbe populations. The use of alternative thresholds/measures should be accompanied by a clear and convincing justification for their use.

**Table 13. Points available for criterion 2F**

|  |  |
| --- | --- |
| Criterion level | Points |
| **Section 1: Maximum of 1 selection from the following:** |  |
| 1 | Preservation of gut microbiome* Evidence of no clinically relevant changes in key groups (e.g. total anaerobes, bifidobacteria, bacteroides, lactobacilli)
 | 60 |
| 2 | Recovery of gut microbiome to pre-treatment levels within 2 weeks of end of treatment* Evidence of no clinically relevant changes in key groups (e.g. total anaerobes, bifidobacteria, bacteroides, lactobacilli) compared with pre-antibiotic treatment levels
 | 30 |
| **Section 2: Maximum of 2 selections from the following:** |  |
| 3 | No overgrowth of commensal facultative bacteria* Evidence of no clinically relevant increase in either lactose fermenting enterobacterales or enterococci
 | 20 |
| 4 | No increased predisposition to colonisation with resistant potential pathogens* Evidence of no clinically relevant increase in any of the following pathogens: *C. difficile*, carbapenemase-producing enterobacterales, glycopeptide-resistant enterococci, extended-spectrum beta-lactamase producers
 | 20 |

Evidence requirements

The 4 types of impact on the gut microbiome can be confirmed by the following evidence sources.

Human in vivo studies, ideally during treatment for infection, that analyse microbiome taxonomic composition in individual samples at baseline, during therapy, at end of treatment and at follow up represent the highest quality of evidence. If evidence is instead supplied from healthy volunteer studies, justification for its clinical relevance should be supplied.

Evidence from clinically relevant artificial gut models is considered the next best alternative because these recreate the critical characteristics and environment of the human bowel. These include triple-stage chemostat models and microphysiological systems. Submissions should specify the approach to quality assurance that was adopted during the development of the evidence and quality standards applied, such as those stipulated by the [Royal College of Pathologists](https://www.rcpath.org/profession/publications/standards-for-microbiology-investigations/quality-related-guidance.html).

Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series)

# Category 3: Health system benefit

# Criterion 3A: Adverse events

Provide evidence of the antimicrobial’s safety profile with respect to serious treatment-emergent adverse events considered by study investigators to be related to the study drug.

**Table 14. Points available for criterion 3A**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Rare or very rare serious treatment-emergent adverse events related to the study drug (less than 1/1000) | 100 |
| 2 | Uncommon serious treatment-emergent adverse events related to the study drug (1/1000 to 1/100) | 65 |
| 3 | Common serious treatment-emergent adverse events related to the study drug (1/100 to 1/10) | 20 |
| 4 | Very common serious treatment-emergent adverse events related to the study drug (greater than 1/10) | 0 |

# Guidance on evidence requirements

Definitions of the frequency of adverse events align with those from the [British National Formulary](https://bnf.nice.org.uk/medicines-guidance/adverse-reactions-to-drugs/). The definition of adverse events categorised as ‘serious’ aligns with that provided by the [International Conference on Harmonization Good Clinical Practice Guideline](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf).

Evidence on adverse events should be extracted from Section 4.8 (‘Undesirable effects’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation and included in the company submission. A draft SmPC will be accepted. If the SmPC for the reference marketing authorisation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel. Safety data from the clinical trials submitted for the reference marketing authorisation application should also be provided.

The minimum clinical trial sample size to achieve the top level of this criterion is 1000 patients. This is required because the highest rate of serious treatment emergent adverse events permissible within this level is 1 in 1000. We recognise that achieving statistical significance to establish frequency of rare or ultra rare adverse event rates requires sample sizes greater than 3,000 patients. However, these requirements are not feasible given that clinical trials of antimicrobials are typically between 500 and 1,500 patients.

# Criterion 3B: Drug-drug interactions

Describe the drug-drug interactions associated with the antimicrobial, and provide supporting evidence. ‘Clinically relevant’ is defined as drug-drug interactions that require clinical or laboratory monitoring, require dose or timing adjustments, or represent contra-indications.

**Table 15. Points available for criterion 3B**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | No clinically relevant drug-drug interactions | 100 |
| 2 | Drug-drug interactions that do not require dose adjustment but require clinical or laboratory monitoring | 65 |
| 3 | Drug-drug interactions that require dose or timing adjustment | 45 |
| 4 | Drug-drug interactions represent contraindication | 0 |

# Guidance on evidence requirements

Evidence on drug-drug interactions with the antimicrobial should be extracted from Sections 4.3 (‘Contraindications’), 4.4 (‘Special warnings and precautions for use’) and 4.5 (‘Interaction with other medicinal products and other forms of interaction’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation and included in the company submission. A draft SmPC will be accepted. If the SmPC for the reference marketing authorisation is not available, then then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

# Criterion 3C: Formulation or delivery of therapy

Describe any benefits of the antimicrobial’s mode of administration compared with current best standard care in the UK, and provide supporting evidence.

An intravenous agent will be considered as ‘low complexity’ if its reconstitution, dilution and administration can be undertaken in wards or clinics. An agent will be considered ‘high complexity’ if its reconstitution, dilution and administration limits use to high-care settings or pharmacy aseptic dispensing.

**Table 16. Points available for criterion 3C**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Formulation or delivery of therapy represents a major improvement in value to the patient and/or health system in addition to intravenous (low complexity) and oral formulations, e.g. delivered via inhalation or topically | 100 |
| 2 | Intravenous (low complexity) and oral formulations | 75 |
| 3 | Intravenous (low complexity) or oral formulation only | 55 |
| 4 | Intravenous (high complexity) formulation only | 0 |

# Guidance on evidence requirements

Evidence on the mode or route of administration of the antimicrobial from Section 4.2 (‘Posology and method of administration’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation should be provided.

Evidence on the handling complexity of the antimicrobial should be extracted from Section 6.6 (‘Special precautions for disposal and other handling’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation and included in the company submission.

A draft SmPC will be accepted. If the SmPC for the reference marketing authorisation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

# Criterion 3D: Dose frequency

Describe how frequently the antimicrobial is administered. If dose frequency varies for different populations, the evaluation panel will consider up to 3 different populations, based on the 3 highest scoring WHO bacterial priority pathogens the product is active against (criterion 1A, Table 2). The evaluation panel will award points for criterion 3D using the highest scoring dose frequency from these 3 populations.

**Table 17. Points available for criterion 3D**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Single or weekly, no observed increase in antimicrobial resistance due to reduced dosing frequency | 100 |
| 2 | Once daily | 95 |
| 3 | Twice daily administrations or continual or long infusion if stable | 65 |
| 4 | Three times daily administration | 50 |
| 5 | Four or more times daily administration | 0 |

# Guidance on evidence requirements

Evidence on the dosing schedule of the antimicrobial should be extracted from Section 4.2 (‘Posology and method of administration’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation and included in the company submission. The panel will only consider dosing schedules permitted within the reference marketing authorisation for the antimicrobial. A draft SmPC will be accepted.

Evidence on whether single or weekly dosing results in ‘no observed increase in antimicrobial resistance’ could be taken from non-UK surveillance data or from phase III clinical trials.

# Criterion 3E: Product stability and storage

Describe the storage and preparation requirements, prior to administration, of the antimicrobial.

**Table 18. Points available for criterion 3E**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Ready to administer with long expiry, no special storage requirements  | 100 |
| 2 | Requires fridge storage or requires reconstitution | 45 |
| 3 | Complex preparation requiring aseptic services | 0 |

# Guidance on evidence requirements

Evidence on the stability and storage requirements of the antimicrobial should be extracted from Section 6.3 (‘Shelf life’) and Section 6.4 (‘Special precautions for storage’) of the Summary of Product Characteristics (SmPC) for the reference marketing authorisation and included in the company submission. A draft SmPC will be accepted. If the SmPC for the reference marketing authorisation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

# Criterion 3F: Monitoring requirements

Describe how frequently patients require therapeutic drug monitoring and/or serum concentration monitoring whilst receiving antimicrobial treatment.

**Table 19. Points available for criterion 3F**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | No therapeutic drug or serum concentration monitoring required | 100 |
| 2 | Therapeutic drug and/or serum concentration monitoring required at 72 hours intervals or longer | 40 |
| 3 | Daily or alternate daily therapeutic drug and/or serum concentration monitoring required | 0 |

# Guidance on evidence requirements

Details on the monitoring requirements of the antimicrobial should be extracted from the Summary of Product Characteristics (SmPC) for the reference marketing authorisation under Section 4.4 (‘Special warnings and precautions for use’) and included in the company submission. A draft SmPC will be accepted. If the SmPC for the reference marketing authorisation is not available, then information extracted from marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel. Safety data from the clinical trials submitted for the reference marketing authorisation application should also be provided.

# Criterion 3G: Reduced hospital-led care

Describe whether the antimicrobial reduces hospital-led care. This can include reductions in hospital admissions, hospital length of stay for treated patients, or the duration of higher-level care management (including provision of outpatient antibacterial therapy). Provide supporting evidence.

**Table 20. Points available for criterion 3G**

|  |  |
| --- | --- |
| Criterion level | Points |
| 1 | Length of stay is reduced or hospital admission is averted compared with current best standard care in the UK | 100 |
| 2 | Duration of higher-level care management (e.g. level 2 or level 3 critical care or augmented care, or provision of outpatient antibacterial therapy) is reduced compared with current best standard care in the UK | 60 |
| 3 | Hospital-led care is non-inferior to current best standard care in the UK. This can include any of the following:* Hospital length of stay
* Hospital admission
* Duration of higher-level care management (e.g. level 2 or level 3 critical care or augmented care, or provision of outpatient antibacterial therapy)
 | 30 |
| 4 | Does not meet any of the above | 0 |

# Guidance on evidence requirements

Direct evidence on the relative effect of an antimicrobial on hospital admissions, hospital length of stay, the duration of higher-level care management or the option to provide outpatient antibacterial therapy treatment should come from the following sources, ordered from highest to lowest methodological quality:

* clinical trials
* registry data analyses
* observational studies
* case series studies.

These studies should preferably be in the UK population. However, studies in non-UK populations will be considered provided that the comparator used in the trial is current best standard care in the UK. Refer to the [NICE real-world evidence framework](https://www.nice.org.uk/corporate/ecd9/chapter/overview) for guidance on the use of real-world evidence.

Evidence should be obtained from a systematic review of the literature. All relevant evidence should be submitted, which can include unpublished studies and conference abstracts. The data from the included studies can be synthesised, but this is not essential. Refer to the [NICE Decision Support Unit’s technical support documents about evidence synthesis.](http://www.nicedsu.org.uk/evidence-synthesis-tsd-series) All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in [Systematic reviews: CRD’s guidance for undertaking reviews in health care](https://www.york.ac.uk/crd/) (University of York Centre for Reviews and Dissemination). Relevant items of the [CONSORT checklist](http://www.consort-statement.org/) should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case. Guidance on the design, conduct and reporting of non-randomised studies is provided in the [NICE real-world evidence framework](https://www.nice.org.uk/about/what-we-do/real-world-evidence-framework).

The evaluation panel will also consider NHS Yellow Cover Documents that support the provision of outpatient antibacterial therapy services. This will be classed as indirect evidence on the reduction in hospital-led care and will not be sufficient to meet criterion levels in the absence of the sources of direct evidence listed above.