# Sample size calculations for NeoSep (23/10/20)

We have assumed the trial will follow a SMART PRACTical design.

At the first randomisation, personalised randomisation lists will be drawn from the list of 8 regimens in the list below, according to three different patterns:

* + Pattern 1: randomise between 1-5 [Kilifi-like]
  + Pattern 2: randomise between 3-8 [Thailand-like]
  + Pattern 3: randomise between 5, 6, 8 (no AMIK] [India ??-like]

We will make two different assumptions about frequencies of patterns: equal pattern frequencies (equal split between Patterns 1-3) or unequal pattern frequencies (50% Pattern 1, 40% Pattern 2, 10% Pattern 3), and carry out separate calculations for each one.

At the second randomisation, personalised randomisation lists will be determined by the patient’s first randomised regimen, as described in the list below. If a patient was randomised under Pattern 3 for the first randomisation, we assume that all regimens including Amik are removed from the second personalised randomisation list.

## Changes from previous calculations dated 16/10/20

* Reversed mortalities in Table 2 have been changed – now derived using direct reversal of regimen effects in Table 1, with no adjustments to ensure mortalities range from 10% to 20%
* Plots from different scenarios are now overlaid

## NeoSep – Strategies for first/second randomisations

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| **Table 1** Randomisation lists at second randomisation and assumed values for true mortality under each first-line/second-line strategy | | | | | | | |
|  | Regimens available at second randomisation | | | | | | |
| Regimen chosen at first randomisation | Cef\* | Fos+  Amik | Flom+  Amik | Fos+  Flom | Pip-Taz | Pip-Taz+  Amik | Mero |
| Amp/Pen+Gent | Yes (20%) | Yes  (18%) | Yes  (17%) | Yes  (17%) | Yes  (17%) | Yes  (15%) | No |
| Cefotaxime | No | Yes  (18%) | Yes  (17%) | Yes  (17%) | Yes  (17%) | Yes  (15%) | Yes  (13%) |
| Fos+Amik | No | No | Yes  (15%) | No | Yes  (15%) | Yes  (13%) | Yes  (11%) |
| Flom+Amik | No | Yes  (15%) | No | No | Yes  (14%) | Yes  (13%) | Yes  (11%) |
| Fos+Flom | No | No | No | No | Yes  (14%) | Yes  (12%) | Yes  (11%) |
| Pip-Taz | No | Yes  (14%) | Yes  (14%) | Yes  (14%) | No | No | Yes  (10%) |
| Pip-Taz+Amik | No | Yes  (13%) | Yes  (13%) | Yes  (13%) | No | No | Yes  (10%) |
| Meropenem‡ | No | No | No | No | No | No | No |

‡ No second randomisation. Assumed value for true mortality is 10%.

Note: The mortality values arise from an additive model for first-line/second-line regimen effects on a logistic scale. The values shown are rounded rather than exact.

* \* CEFTRIAXONE OR CEFOTAXIME AS LOCAL PREFERENCE
* 2020 IDSA GUIDANCE FOR TARGETED THERAPY SUGGESTS PIP-TAZ SHOULD BE AVOIDED FOR ALL ESBL-E (AND CEFTRIAXONE NON-SUSCEPTIBLE) E.COLI AND KLEBS INFECTIONS EXCEPT CYSTITIS EVEN IF PIPTAZ SUSCEPTIBLE IN VITRO – ALL ESBL INFECTIONS EXCEPT CYSTITIS SHOULD NOW BE TREATED WITH CARBAPENEMS.
* 2020 IDSA GUIDANCE FOR PROVEN CRE RECOMMEND CEFTAZ-AVI, MERO-VABOR, IMI-RELE. IF PROVEN OR LIKELY NDM/OXA-48 USE CEFTAZ-AVI+AZTREONAM OR CEFIDEROCOL. NO ROLE FOR POLYMIXINS.

<https://www.idsociety.org/practice-guideline/amr-guidance/>

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2** Randomisation lists at second randomisation and *reversed* assumed values for true mortality under each first-line/second-line strategy | | | | | | | |
|  | Regimens available at second randomisation | | | | | | |
| Regimen chosen at first randomisation | Cef\* | Fos+  Amik | Flom+  Amik | Fos+  Flom | Pip-Taz | Pip-Taz+  Amik | Mero |
| Amp/Pen+Gent | Yes (6%) | Yes  (7%) | Yes  (8%) | Yes  (8%) | Yes  (9%) | Yes  (9%) | No |
| Cefotaxime | No | Yes  (11%) | Yes  (12%) | Yes  (13%) | Yes  (13%) | Yes  (13%) | Yes  (15%) |
| Fos+Amik | No | No | Yes  (13%) | No | Yes  (14%) | Yes  (14%) | Yes  (16%) |
| Flom+Amik | No | Yes  (12%) | No | No | Yes  (14%) | Yes  (15%) | Yes  (17%) |
| Fos+Flom | No | No | No | No | Yes  (15%) | Yes  (15%) | Yes  (17%) |
| Pip-Taz | No | Yes  (13%) | Yes  (15%) | Yes  (15%) | No | No | Yes  (17%) |
| Pip-Taz+Amik | No | Yes  (15%) | Yes  (17%) | Yes  (17%) | No | No | Yes  (20%) |
| Meropenem‡ | No | No | No | No | No | No | No |

‡ No second randomisation. Assumed value for true mortality is 20%.

Note: These mortality values were obtained by reversing the sets of first-line/second-line regimen effects used in Table 1. Because many row/column combinations are not allowed, reversing the regimen effects produces a different collection of mortality values, ranging now from 6% to 20%. The values shown are rounded rather than exact.

## Assumptions informing sample size calculations

Calculations assume a primary endpoint of mortality at 28 days. 28 day mortality for babies eligible for recruitment to NeoSep is expected to be 15-30% across sites (no site effects included in calculations).

Following treatment under the first-line/second-line strategies described above, 28 day mortality is expected to vary from 10-20% across strategies. In the sample size calculations, fixed values for first-line and second-line regimen effects have been selected to achieve this variation (Tables 1 and 2).

Early mortality before second randomisation has been assumed to be 5% (informed by NeoOBS data). We have not assumed early mortality to vary across regimens.

In the absence of early mortality, percentages of babies switching to a randomised second-line treatment have been assumed to be 25% or 50% - separate calculations have been carried out for these values.

## Analysis

In analysis of the simulated data, we have performed comparisons of first-line/second-line strategies (e.g. regimens 1 followed by 2, 1 followed by 3, 3 followed by 6). In total, there are 32 first-line/second-line strategies, including the strategy of giving meropenem followed by no second-line randomisation.

We have chosen to compare first-line/second-line strategies rather than performing separate comparisons of first-line treatments and second-line treatments. The aim of the simulations is to evaluate how the decisions made for future patients would be informed by all information obtained from the trial rather than by the first-line or second-line analysis alone.

### Technical notes

Data were analysed using a logistic model including main effects for first-line and second-line treatments and adjustment for pattern at first randomisation. No adjustment for pattern at second randomisation is required since this is determined by first randomised treatment and by pattern at first randomisation.

For individuals who didn’t require a second randomisation (early mortality or no switch required), cloned records have been created to represent regimens they could have received if randomised a second time, and an inverse probability weighting approach has been taken in analysis.

## Results

The plots below display results corresponding to sample sizes between 500 and 3000. For each scenario, 1000 simulations were carried out.

Results presented are:

* average reduction in % mortality from sample information as percentage of reduction from perfect information
* % success: chosen first-line/second-line strategy based on sample information was within 2% of the best strategy
* % success: chosen first-line/second-line strategy based on sample information was within 1% of the best strategy
* % success: chosen first-line/second-line strategy based on sample information was at least 2% better than the worst regimen in the pattern
* % with improvement: chosen strategy based on sample information was better than a randomly chosen strategy
* % with improvement: chosen strategy based on sample information was better than the worst regimen in the pattern

95% CIs reflect Monte Carlo error across 1000 simulated data sets.



Average reduction in % mortality from sample information as percentage of reduction from perfect information



% success: chosen strategy is within 2% of the best strategy



% success: chosen strategy is within 1% of the best strategy



% success: chosen strategy is at least 2% better than worst regimen in pattern



% with improvement: chosen strategy better than a randomly chosen strategy



% with improvement: chosen strategy better than worst regimen in pattern

## Appendix

## Data generating model used in simulations

Participants are allocated to first-randomisation patterns in proportions of 1/3 per pattern.

Participant is randomly (equiprobably) allocated to one treatment .

If a switch to second-line treatment is required, participant is randomly (equiprobably) allocated to one treatment , where is the appropriate second-randomisation pattern.

Outcome is with probability where

## Decisions evaluated

Decision for future individual eligible for first-line/second-line strategies in the set :

1. No information: strategy is randomly drawn from .
2. Sample information: treatment is chosen as the that minimises (estimated mortality based on analysing the data in the sample).
3. Perfect information: treatment is chosen as the that minimises (true mortality based on assumed model parameters).