Supplementary material 2 - additional information relating to structured expert elicitation

1. Structured expert elicitation: background information provided to clinicians

1.1 Introduction

NICE, NHS England and NHS Improvement have commissioned a project to assess the feasibility of innovative models for reimbursing antimicrobials.

As part of the project, the University of Sheffield and the University of York are modelling outcomes of two antimicrobials that target infections caused by carbapenem-resistant gram negative bacteria. For this modelling we are focusing on patients with infections caused by the following pathogens:

- Cefiderocol (Fetcroja) targetting carbapenem-producing enterobacterales (CPE) and pseudomonas with metalo-beta-lactamase (MBL); and
- Ceftazidime with avibactam (CAZ-AVI, Zavicefta) targeting CPE with OXA-48.

This modelling work and subsequent NICE Committee deliberations will provide guidance on the value of each product to the NHS.

There are several model inputs for which data are limited or unavailable. As an alternative we require your expert opinion to inform these inputs. We are also interested in how uncertain you are about your opinions. The training seminar gave you guidance on how to express your uncertainty. We will use this approach here.

To begin, please click on the 'About you' tab at the top of the screen and proceed as advised thereafter.

1.2 Background information

We are interested in outcomes for patients with Hospital Acquired Pneumonia (HAP), Ventilator Associated Pneumonia (VAP), and complicated urinary tract infections (cUTIs) caused by carbapenem-resistant gram negative bacteria. Specifically, we are interested in outcomes following microbiology-directed treatment for patients with an infection caused by CPE with an OXA-48 or MBL resistance mechanism, or pseudomonas with a MBL resistance mechanism.

1.3 What do we mean by microbiology-directed treatment?

Patients in the microbiology-directed setting may have received empiric treatment with other antimicrobials prior to receiving microbiology results but require a change of treatment. This could be for a range of reasons including poor response to empiric treatment or adverse events requiring discontinuation of empiric treatment. Once the microbiology results are available, patients are assumed to be eligible to receive CAZ-AVI or cefiderocol (if found to be susceptible to them) if they meet either of the following criteria:

- Patients are susceptible only to colistin or aminoglycosides, and the new treatments offer improved safety.

- Patients are not susceptible to any existing treatment options, and the new treatments offer improved effectiveness and, possibly, safety.

Without the new treatments, patients who are not susceptible to any existing treatment options would be assumed to receive multi-drug salvage regimens.

1.4 Outcomes of interest

For patients with HAP, VAP or cUTIs, whose infection is caused by CPE with an OXA-48 or MBL resistance mechanism or pseudomonas with a MBL resistance mechanism, and whose treatment is informed by microbiology results, we are interested in outcomes depending on whether the infectious pathogen is susceptible to treatment.

We will assume that outcomes only depend on whether a patient is susceptible to treatment or not, and not to the specific treatment given. We therefore leave aside toxicity issues and differing risks of adverse events across treatments for the moment. We also assume that these patients will not experience acute kidney injury.

Note that in this scenario, patients who are classified as not susceptible to any treatment are assumed to receive multi-drug salvage regimens.

The outcomes we are interested in are 30-day mortality, length of stay in hospital, and the type of ward these patients would stay on in hospital.

1.5 Existing literature

We are not aware of any literature reporting our outcomes of interest in susceptible and not susceptible patients in the microbiology-directed setting, for patients with HAP, VAP, cUTIs caused by carbapenem-resistant gram negative bacteria.
We are therefore asking you to estimate these outcomes in this exercise and tell us how uncertain you are about your estimates.

As background we have identified several related studies that may help inform your answers, although they are not directly addressing the outcomes of interest. In these studies, infecting pathogens were not confirmed to be susceptible to the antibiotics administered (cefiderocol or CAZ-AVI); however, in our assessment they are likely to have been susceptible.

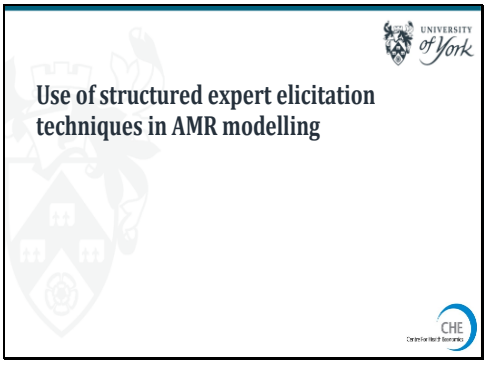
These studies are summarised in the table below.

Study	**Site of infection and organism**	**Pathogen**	**Treatment received**	**Treatment history**	**Patient characteristics (mean)**	**Outcomes: HAP/VAP/ nosocomial pneumonia**	**Outcomes: cUTIs**
APEKs-NP	HAP (n=59) VAP (n=59) HCAP (n=27)	Infections caused by Gram negative pathogens. Excluded patients known to have carbapenem-resistant pathogens at the time of ransomisation.	Cefiderocol	33% had had empiric treatment failure	Age = 64.6 APACHE II = 16.0 SOFA = 4.7 CCI = NR	14-day mortality HAP: 10.2% VAP: 15% Total: 12.4% 28-day mortality Total:21.0%	NA
CREDIBLE-CR	Nosocomial pneumonia (n=40) cUTIs (n=17) bloodstream infections or sepsis (n=44)	Infections with evidence of a carbapenem-resistant Gram negative pathogen	Cefiderocol	57% had had empiric treatment failure	Mean age = 63.1 APACHE II = 15.3 SOFA = 5.1 CCI = 5.5	Nosocomial pneumonia 28-day mort: 33%	28-day mort: 12%
REPRISE	cUTI (n=152)	Infections caused by ceftazidime-resistant Gram negative pathogens	CAZ-AVI	50% had received prior empiric treatment	Mean age = 64.3 APACHE II = NR SOFA = NR CCI = NR	NA	28-day mort: 2.1%
REPROVE	HAP/VAP (ΩΑΠ ν=118;΄νον-ΩΑΠ ν=238)	Excluded infections caused by Gram positive pathogens only or other pathogens not expected to respond to CAZ-AVI and/or meropenem	CAZ-AVI	34% had received no prior antibiotics	Mean age = 62.4 APACHE II = 14.5 SOFA = NR CCI = NR	28-day mort: 8.4%	NA

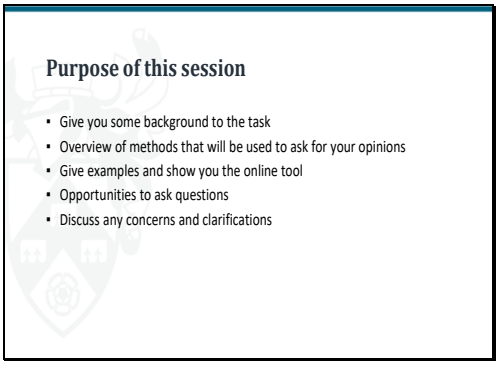
HAP =hospital acquired pneumonia; VAP = ventilator-associated pneumonia; HCAP = healthcare-associated pneumonia; cUTI = complicated urinary tract infection; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; CCI = Charlson Comorbidity Index; NR = not reported.

2. Training slides for expert elicitation

Slide 1



Slide 2



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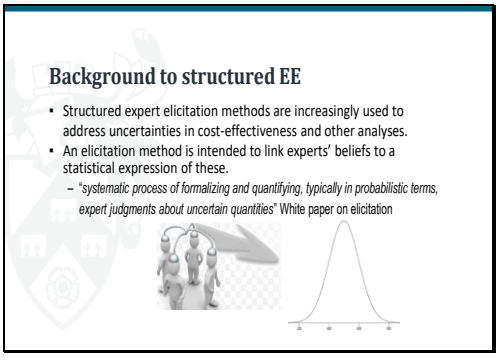


Slide 4

Uncertainty in health care decision making

- Focus on capturing and understanding uncertainty
- Uncertainty relates to many types evidence used to inform health care decision making
  - The evidence itself may be uncertain, for example wide confidence intervals
  - Unsure how generalizable the evidence is the population in question
  - There may be sparse or entirely absent empirical data
- Uncertainty is not bad
  - To make 'better' decisions we need to quantify this uncertainty
  - Incorporate uncertainty into our decision making processes

Slide 5

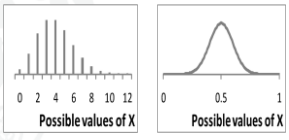
Uncertainty in beliefs

- Rarely absolutely certain about degree of belief
- Subjective & personal
  - degree of belief in an uncertain proposition
  - reflect epistemic uncertainties (imperfect knowledge)
- Good elicitation should eradicate bias, irrationality…
  - But inevitably, the quantities elicited are personal

Slide 6

Communicating uncertainty

- Aim to represent the degree of belief experts have about uncertain quantities
  - Experts encouraged to 'reveal' this uncertainty



Slide 7

In the context of understanding the value of Antimicrobials

- Uncertainties include:
  - Prognosis
  - Risk of infection
  - The efficacy of treatments
  - Estimates of the eligible population
  - Transmission value
- A cost-effectiveness model is used to assemble all current information on specific treatments
  - For many of these uncertainties there are empirical data available to populate a cost-effectiveness model
  - For some uncertainties we are asking experts to provide us with their estimates

Slide 8

What we will ask you to do in the AMR elicitation task

- Answer questions relating to quantities required to populate our cost-effectiveness models
  - We will ask you about your uncertainty (methods shown later)
  - A few general questions about you
- Give you three working days to complete this task
  - Should take around an hour
- We will assemble the information you provide and feed this back to you
  - An opportunity to revise your responses
  - Final submission of your responses
- All responses will be anonymised

Slide 9

How will I be asked to express uncertainty?

- Here I will talk about uncertainty expressed as **probabilities/proportions**
  - In the task you may be asked about other quantities – I will give examples later
- Here, the probability of an event happening is a number between 0 and 100%.
  - 0% -- no chance it will happen
  - 100% -- it is certain to happen
  - 50% -- it is equally likely to happen and not to happen
- The probability of an event happening is 100 minus the probability of it not happening
- These probabilities represent degrees of belief

Slide 10

How do I start to consider how uncertain I am?

- A probability can, in theory, take any value >0 and <100
- The most likely value can be narrowed down to a range of plausible values
  - I am very confident that the probability of response is not less than 20%, and that it is not more than 80%
- You may also believe that the probability of response is more likely to be between 40 and 60% than it is to be between 20 and 40%, or between 60 and 80%.

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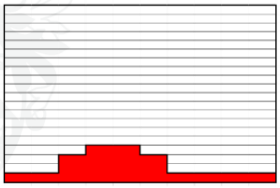
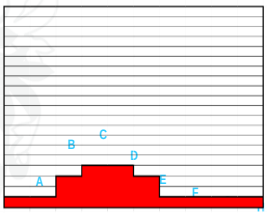
Slide 11

- **You can express your beliefs using a histogram (chips and bins) such as this one:**



Slide 12

What do different shape histograms mean?



0-20 are unlikely but possible

20-30 is three times more likely than 0-20 or 60-100%

30-50% is the most likely probability of response

30-50 is four times more likely than 60-100

60-100 are unlikely but possible

.....and so on

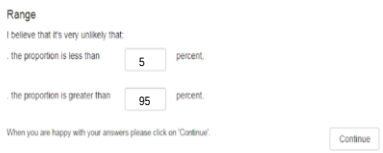
Slide 13

What will I be asked to do this here?

- For a particular quantity of interest, you will first be asked to give a plausible range:
  - Your lowest plausible proportion (minimum) - a value such that you believe that there is a 1% probability that the value is less than this.
  - Your highest plausible proportion (maximum) - a value, such that you believe that there is a 1% probability that the value is more than this.
  - So you believe that there is 98% probability between the lowest and the highest values.
- Test your range by imagining that somebody gives a value that is outside your plausible range (i.e. less than your minimum or more than your maximum).
  - Your reaction should be that the person has misunderstood or misremembered, i.e. you are very confident that you have chosen the right range!

Slide 14

Plausible range



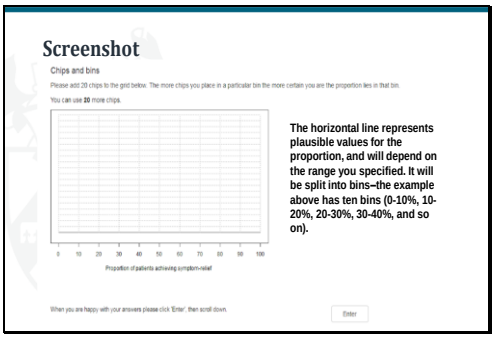
Slide 15

Filling in the chips and bins (histogram)

- After giving your plausible range, you will then be required to fill in a histogram. The range of possible values that appear are determined by the range you specified.
- You will be given a number of 'chips' to place in the bins to express your beliefs about the plausibility of values within the range you have specified.
  - There are a different number of chips depending on the range you give

Slide 16

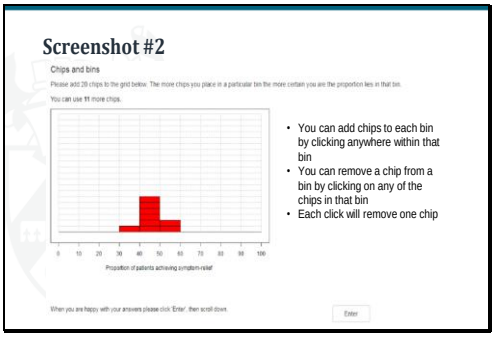
Screenshot



The horizontal line represents plausible values for the proportion, and will depend on the range you specified. It will be split into bins–the example above has ten bins (0-10%, 10-20%, 20-30%, 30-40%, and so on).

Slide 17

Screenshot #2



- You can add chips to each bin by clicking anywhere within that bin
- You can remove a chip from a bin by clicking on any of the chips in that bin
- Each click will remove one chip

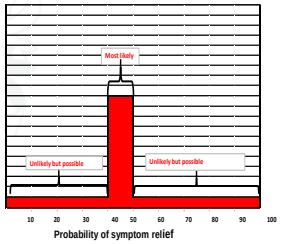
Slide 18

Opportunity to look at the app used for the AMR elicitation

Slide 19

Could be quite certain about a particular value

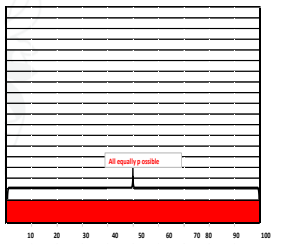
- Grid *could* look like this:



Slide 20

Could be uncertain about the value

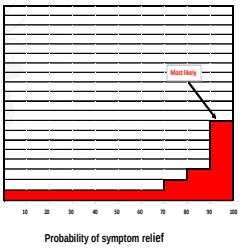
- Grid *could* look like this:



Slide 21

Or….

- Grid *could* look like this:

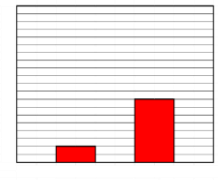


Slide 22

Its important to realise…

- Because we are asking about the most likely value for a particular quantity and the uncertainty around this there is unlikely to be a rationale for breaks in the bins

i.e. would not assign 20% to 20-40,
0% to 40-60 and
80% to 60 to 80



Slide 23

All this seems a bit complicated!!!

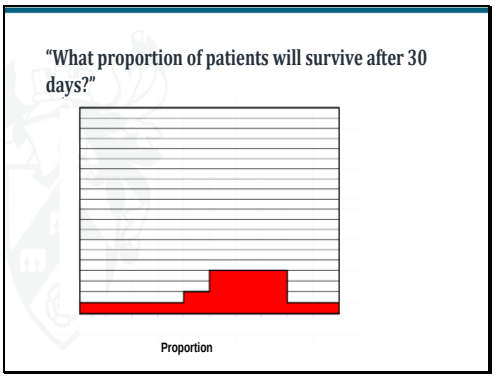
Some examples may help

Slide 24

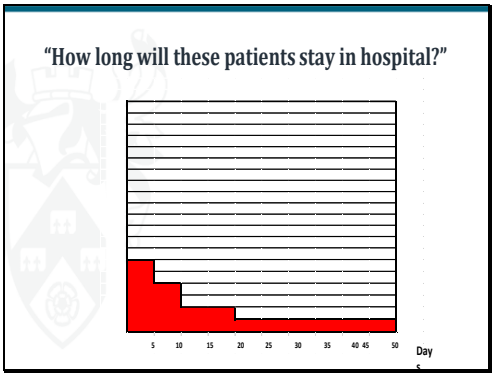
Here are some examples:

- "What proportion of patients will survive after 30 days?"
- "How long will these patients stay in hospital?"

Slide 25



Slide 26



Slide 27

Things to be aware of

There are ways in which we process and express information that can lead to potential biases, in particular:

- Overconfidence
  - You may overstate how certain you are about a particular value for a quantity. Its OK to be uncertain
- Under confidence
  - Try not to be too cautious about what you do not about a quantity, that is don't be driven to express that you are more uncertain, when you actually have a strong belief that a quantity takes a particular value