ADDIS MCDA tutorial

Contents

💡 Throughout this tutorial we also mention features only available in the Enterprise edition of ADDIS/MCDA (see here). These features are marked with a bar on the left of the paragraphs, like so:

> Marked enterprise features.

Tutorial 1: manual data entry

This tutorial guides you through the process of manually entering data, from which you will be able to create your own effects tables.

Subjects covered

- Manual data entry interface
- Defining criteria and alternatives
- Specifying references
- Filling in the data entry table

Example effects table

The data that you are going to enter in this tutorial is taken from the effects table for lixisenatide as included in the EMA Guidance document for critical assessment reports (see page 72). For didactic purposes, we are going to work with a simplified version of that table which includes HbA1c as a favourable effect and nausea as an unfavourable effect (Figure 1).

Sign in to your organisation's ADDIS/MCDA.

☞ Open your browser and navigate to the URL where your organisation provides ADDIS/MCDA. Use your username and password to sign in. You will be redirected to your personal homepage, containing your previously created workspaces, both finished and unfinished (if any).

Create a new workspace

☞ Press the 'Add workspace' button, select the option 'Create new workspace', and press the 'Add' button. This leads to the manual entry process.

🎓 A workspace contains the clinical efficacy and safety data that you have entered for a particular benefit-risk assessment. Within a workspace you can build effects tables and perform quantitative benefit-risk analyses. Existing workspaces are opened by clicking on their name, or navigating to their URL directly via a link or bookmark. Workspaces can only be accessed by their owner and whoever the owner has granted access.

💡 In this tutorial we cover the manual workspace creation process; besides this you can also create workspaces based on example data uploaded by the ADDIS team, and upload JSON files exported by you or another user.

Effect	Description	U	LIX	PBO	Uncertainties / Strength of evidence	Reference
Favourable Effects						
HbA1c	Mean change in HbA1c from baseline	%	-0.83 (-0.91, -0.75)	-0.39 (-0.51, -0.28)	**Unc:** The effect of lixisenatide was more pronounced in Asian patients compared to Caucasian patients. The lower effect in Caucasians is partly explained by a large placebo effect especially in some geographical regions.	Pooled data from EFC6014 and EFC10743
			-0.82 (-0.91, -0.73)	-0.10 (-0.24, 0.04)		EFC6015
Unfavourable Effects						
Nausea	Incidence of nausea	%	26.9	7.3		pooled data from all phase 2/3 controlled studies

Figure 1: Simplified effects table for lixisenatide, a treatment for type 2 diabetes mellitus

Enter general information

☞ Enter a descriptive title in the 'Workspace title' field at the top of the page. For example, "lixisenatide data entry tutorial".

☞ Enter the indication and other relevant context for your assessment in the 'Therapeutic context' field. For example, "Assessment of lixisenatide for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients not adequately controlled on oral antidiabetics."

💡 Any changes you make are automatically saved. You can select this in-progress workspace from your personal homepage later, and continue where

you left off. You can navigate back to your home page by pressing the mcda.drugis.org link on the menu bar at the top-left of the screen.

Criteria and favourability

🎓 Criteria are the clinical efficacy and safety outcomes in terms of which the treatments under consideration are evaluated. A criterion has a name (a short identifier, such as "HbA1c" or "Nausea"), and a description. The description can be used to give more detail about the criterion, such as a specification of how the selected outcome effect is measured statistically. For example, for "HbA1c" this could be "mean change of HbA1c from baseline" or "proportion of patients with a normal HbA1c value at week 24".

🎓 For regulatory purposes, criteria can additionally be classified as favourable or unfavourable, with favourable criteria being ones where the new treatment under consideration outperforms the status quo.

☞ The effects table for lixisenatide divides the criteria into favourable and unfavourable effects. To enable this classification, ensure that the 'Use favourability' box below the 'Criteria' heading is checked.

🎓 A fresh workspace is pre-initialised to include two criteria and two alternatives by default, with generic names. You can add further alternatives, criteria and references using the '+' buttons, and delete them with the garbage bin icons.

Add the HbA1c criterion

☞ Change 'criterion 1' to 'HbA1c' by clicking its title and changing the value in the text box. Similarly, change the description to be 'Mean change of HbaA1c from baseline'.

Add two references for HbA1c

🎓 For each criterion, there can be one or more references from which summary statistics or treatment effect estimates are taken. A reference can be a single pivotal study but could also be a pooled analysis, such as a combined safety pool or a (network-) meta-analysis. Its origins are specified via its

name (the 'Reference' field) and optionally its URL.

☞ For the HbA1c criterion, edit the existing reference, by clicking on the last cell in the row, and fill in the dialog to be "Pooled data from EFC6014 and EFC10743", leaving the 'Reference URL' field empty. After closing the dialog, the reference should now display your changes. Click the 'Add a reference' button (the '+' symbol) just below this row. A second reference row will appear. Edit this one so the reference is "EFC6015", again leaving the 'Reference URL' field empty.

Add nausea as an unfavourable effect

☞ Edit 'criterion 2' to be called 'Nausea' and set its description to 'Incidence of nausea'. Then, change it from a favourable to an unfavourable effect by clicking the icon on the left of the row, with the thumb pointing down.

☞ Change the reference to "Pooled data from all phase 2/3 controlled studies". There are no further references for this criterion.

Add lixisenatide and placebo as alternatives

☞ Rename 'alternative 1' by clicking on it and entering 'lixisenatide' in the text box. Rename 'alternative 2' to 'placebo'.

Set the units of measurement

☞ We can set the unit of measurement for each reference. To do so, click on the 'Unit of measurement' cell.

☞ For 'HbA1c/Pooled data', leave the type on 'Custom' and add the Label 'Percentage point'. Do the same for 'HbA1c/EFC6015'.

☞ For the Nausea reference, select 'Proportion (percentage)' as the unit of measurement.

Proceed to data entry

Effect and Distribution modes

💡 Data entry is split into two modes – Effect and Distribution – and you can switch freely between them using the dropdown above the effects table. In this tutorial, we will be mainly using the Effect mode.

🎓 Data about effects can be entered either as effects or distributions. An overview of the various data entry possibilities is provided in the Appendix to Tutorial 1.

Add Strength of evidence/Uncertainties

🎓 The 'Uncertainties' and 'Strength of evidence' fields describe any strengths and weaknesses of the study design, quality of the data collection and analysis, generalizability of the study findings, etc.

☞ We will add the following Uncertainty to the 'HbA1c/Pooled data' reference: "The effect of lixisenatide was more pronounced in Asian patients compared to Caucasian patients. The lower effect in Caucasians is partly explained by a large placebo effect especially in some geographical regions." To do so, click the 'Unc' text and fill in the text box.

Enter data

☞ Click on the 'No value entered' text in the cell for HbA1c's 'pooled data from EFC6014 and EFC10743' row and lixisenatide column. Fill out the dialog as shown in Figure 2, and click anywhere on the page outside of the dialog to close it.
☞ Proceed to fill out the remaining three cells for HbA1c with the point estimates and 95% confidence intervals from Figure 1.

☞ Similarly, fill out the cells for Nausea with the values from Figure 1, selecting 'Value' as the input parameter. Your final data entry table should look like Figure 3.
💡 If required, cells can be left empty by choosing the 'Empty cell' as the input parameter.

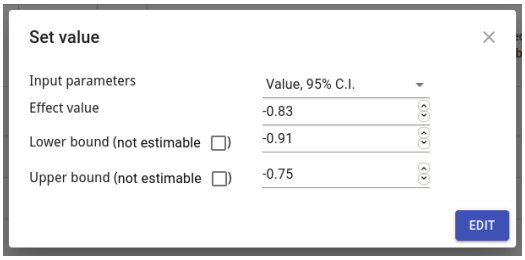


Figure 2: Data entry dialog for HbA1c.

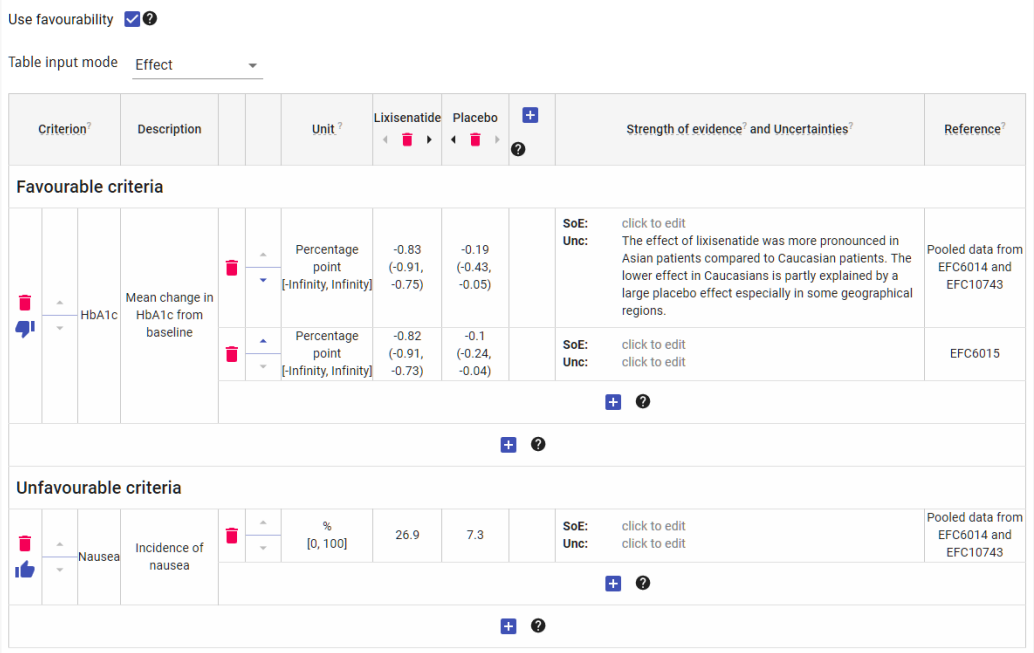


Figure 3: Final data entry table for lixisenatide.

Generate distributions

☞ If a user wishes to work with distributions and perform SMAA analyses but the data is provided as effects only, it is possible to automatically generate the distributions. To do so, click the 'Generate distributions' button. Doing this will take you to the Distributions view, where the automatically generated distributions are shown. Please see the Appendix to Tutorial 1 to see which effect input types are converted into which distribution types.

Finalize entry

You have now finished preparing your effects table for analysis.

☞ Click 'Done' and you will go to the overview page of your newly-created workspace where you will find the entered effects table.

🎓 After finishing the manual entry process, cosmetic properties such as names and descriptions can still be edited, and the criteria can be re-ordered using the arrow buttons. However, to prevent breaking the analyses that are based on them, measurements cannot be modified. Changing measurements can be done by creating a copy of the workspace on your homepage. This begins a new manual entry process as detailed above, but all criteria, alternatives and measurements are already filled out based on the old workspace, and can be changed at will.

Export and share with others

☞ On your newly-created workspace, click 'Download workspace' in the top-left to save a .json file which contains all the data you just entered. When creating a new workspace, you can upload this file (using the 'local file' option) and the new workspace will contain a copy of your data.

💡 Sending this file via e.g. email to someone else is the recommended way to share workspace data with other users. In the Enterprise version of our software, you can also grant access to others directly within the application.

Appendix to Tutorial 1: reference characteristics and data entry options

A treatment effect is a statistical parameter that describes how a given treatment affects the distribution of a criterion in the target population (i.e., all patients for which the evaluated treatment is indicated). The representation of that parameter's uncertainty in the effects table depends on the specified characteristics of the row's reference. Indicating that the input type is 'Distribution' corresponds to a Bayesian perspective, where the uncertainty is quantified by means of probability distributions. The option 'Effect' corresponds to a frequentist perspective where parameters are treated as fixed but unknown constants for which point and interval estimates (e.g., 95% confidence intervals) are provided.

Types of distributions (Bayesian)

Distributions can be specified directly by choosing a type of distribution and entering its parameters, or derived indirectly from summary statistics from a clinical study (option 'Generate distributions'). When this latter option is selected, a Bayesian posterior distribution (i.e., a beta distribution for the event probability of a dichotomous outcome variable and a normal distribution for the mean of a continuous outcome variable) is estimated from the summary statistics supplied by the user and a reference prior set by the system.

The following types of distribution are supported:

- Beta
- Normal
- Gamma
- Value (i.e., degenerate distribution that always results in the same value)
- Range

Distributions of the type 'Value' and 'Range' can be input either as percentages, decimals, or neither, see 'Units of Measurement,' below.

Types of effects (Frequentist)

The following data entry options are currently available for effects:

- Value
- Value, 95% confidence interval
- Range

These effects can be input either as percentages, decimals, or neither, see 'Units of Measurement', below.

Unit of measurement

The following units of measurement are supported:

- Custom: you can input a custom label and any lower and upper bounds.
- Proportion (decimal): label will be set to 'Proportion', and lower and upper bounds to 0 and 1, respectively.
- Proportion (percentage): label will be set to '%', and lower and upper bounds to 0 and 100, respectively.

You can switch between 'Percentages' and 'Decimals' views by changing the workspace settings (accessed by clicking the 'settings' button at the top right of the screen for any finished workspace). This will automatically scale the values were possible, i.e. datasources with either 'Proportion (decimal)' or 'Proportion (percentage)' unit of measurement.

The user can enter '%' as a label for a custom unit of measurement for a reference. However, switching between 'Percentages' and 'Decimals' views will not scale the values in this case.

Tutorial 2: effects table building

This tutorial guides you through the process of making analysable effects tables out of larger datasets.

Subjects covered

- Problem definition interface
- Creating effects tables of subsets of your measurements data
- Switching between effects tables

Example effects table

The data that you are going to enter in this tutorial is taken from the effects table for lixisenatide as included in the EMA Guidance document for critical assessment reports (see page 72). We use a similar table to the previous tutorial, with one more criterion and alternative.

Sign in to your organisation's ADDIS/MCDA.

☞ Open your browser and navigate to the URL where your organisation provides ADDIS/MCDA. Use your username and password to sign in. You will be redirected to your personal homepage, containing your previously created workspaces, both finished and unfinished (if any).

Create a new workspace

☞ Press the 'Create workspace' button, click 'Select tutorial workspace', load the 'Lixisenatide simplified' example, and press the 'Add' button. This takes you to the overview screen. Take a moment to look at the criteria, alternatives, and data sources.

Create an analysable effects table

☞ Click on the 'Problem definition' tab. Note that the currently-selected problem (in the dropdown at the top of the screen) is the 'Default' problem. This problem is always automatically generated by the system and includes

all criteria, alternatives, and data sources shown on the 'Overview' tab.

🎓 A 'problem' is our term for an analysable selection of criteria, alternatives, and data sources from those available in the workspace. This selection can include everything in the workspace, but several restrictions apply:

- Only one data source can be selected per criterion
- No missing measurements (empty cells) are allowed for any combination of the selected criteria/alternatives

An exception is the 'Default' problem, which may contain multiple data sources as well as empty cells. Should this be the case, the 'Default' problem is considered to be not analysable, resulting in an inactive 'Preferences' tab. Hovering your mouse over the 'Preferences' tab will then show a tooltip explaining why this tab is inactive.
☞ Click the '+' icon under the 'Problem' dropdown (Figure 4). This opens the problem creation dialog.

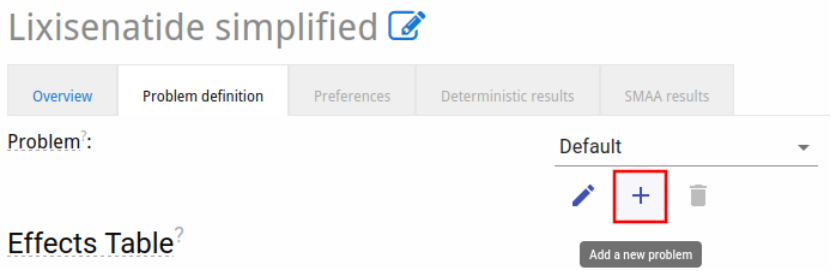


Figure 4: Problem creation button

☞ Scroll down and take a look at the warnings the bottom of the dialog. These explain why the current selection of criteria, alternatives, and data sources is not analysable. To make the effects table analysable, first, deselect the Exenatide criterion and then deselect the data source rows for EFC6019. This should cause the warning about missing values to disappear. Next, deselect the data source rows for EFC6015, so that we end up with a lixisenatide/placebo comparison based on pooled data EFC6014 and EFC10743 for HbA1c and Hypoglycaemia. Now the warning about multiple data sources should have disappeared (Figure 5). The controls for setting the scale ranges (the breadth of possible values to asses on the 'Preferences' tab, see next

tutorial) are now also accessible; these are not part of this tutorial. Give the problem an informative name such as 'Lixi-PBO pooled' and click 'Add' at the bottom of the dialog.

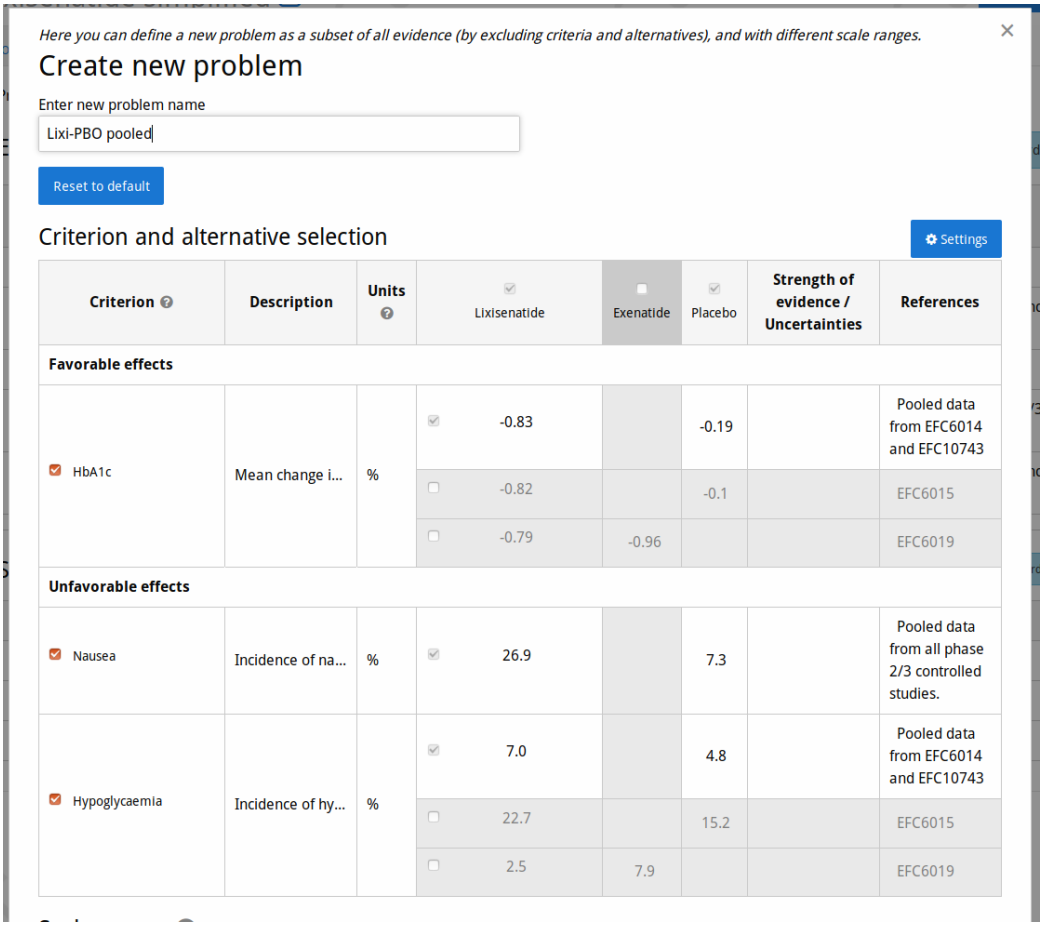


Figure 5: Creating a problem

☞ Observe the effects table for the new problem. Note that the 'Preferences' tab has now become enabled. That tab and the ones to its right are the subject of the following tutorials.

Create more effects tables

☞ Create another problem, this time selecting EFC6015 as data source for HbA1c and Hypoglycaemia, and indicate this fact in the title.

💡 When creating a new problem, the initially-selected criteria and alternatives are based on those of the current problem. The initial 'Default' problem always has everything selected, and thus may not be usable for analysis.

☞ Create another problem, but now to compare Lixisenatide and Exenatide. Note that, since there is no data source with measurements for Nausea for both alternatives, this problem must omit Nausea as a criterion.

☞ Use the 'Problem' dropdown at the top of the tab to switch between your effects tables. Observe that the effects table and browser URL changes whenever you switch problem.

🎓 Creating a set of problems that all look at different aspects of your workspace's data lets you contrast the alternatives in different ways. For each problem you can then define a further set of scenarios with different preferences regarding the importance of your criteria, and compare their benefit-risk balances (subject of the next tutorial).

Workspace and view settings

☞ Click on the 'settings' button at the top of the tab (Figure 3). This lets you customise your view of the effects table and measurements in general. Take a moment to study the different settings you can choose. Play with the top three settings by changing their value and clicking 'Save', and observe the results. What should happen:

- Changing to Median/Mode does nothing (this only applies when the values shown in the effects table are sampled from probability distributions).
- Changing the 'Measurements display mode' from 'Entered effects' to 'Values used in deterministic analysis' shows the values as they will be used for calculating the deterministic results. Changing to 'Entered distributions' shows the distributions and their parameters used for calculating the SMAA results. For this example no distributions where entered and this option is not availbable.

- Changing to 'Values used in SMAA' shows the 95% confidence interval calculated from the distributions, however since we've only entered effects for this example, it will show the point estimate of those effects.
- Changing between percentages and decimals changes the shown values and units for Nausea and Hypoclycaemia but not HbA1c (this setting only affects dichotomous criteria).

☞ Uncheck e.g. the 'Description' and 'Uncertainties / Strength of evidence' checkboxes in the bottom section of the settings dialog to make the effects table more compact. Click 'Save' and study the result.

Export effects table

☞ Open a rich text editor, such as MS Word, LibreOffice or Google Docs. Choose one of your effect tables, and click the 'Copy to clipboard' button (Figure 6). Now go to the editor and paste the selection in there. This should result in a structured table similar to the one in the browser. Depending on your editor and its settings, you may want to adjust things like whether there are borders around cells in your editor's table settings.

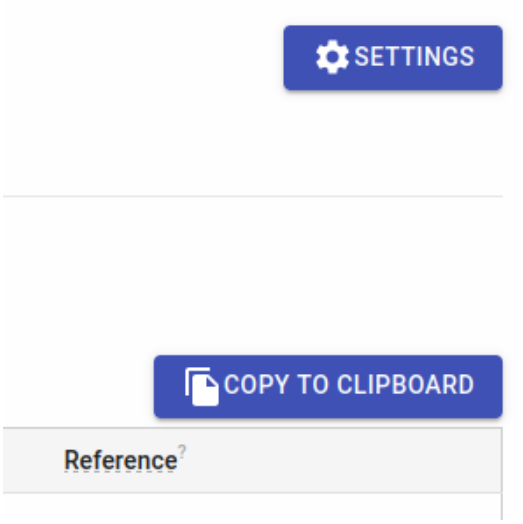


Figure 6: Settings and copy buttons

Final words

We hope that this tutorial has demonstrated adequately how to go from a wider data set to a smaller effects table that can be used to analytically study the benefit-risk balance of selected alternatives for selected criteria. We've also shown how to switch between such problems at will. Finally, we've shown how to change several aspects of how the effects table is displayed, and how to export your effects table to text editors e.g. for report writing.

Tutorial 3: multi-criteria decision analysis

Subjects covered

- Creating a new workspace based on an example dataset
- Exploring different methods for preference elicitation, that is, quantifying how important the benefits and risks of treatments are to you
- Seeing how these preferences impact the relative value of the evaluated treatments

Sign in to your organisation's ADDIS/MCDA.

☞ Open your browser and navigate to the URL where your organisation provides ADDIS/MCDA. Use your username and password to sign in. You will be redirected to your personal homepage, containing your previously created workspaces, both finished and unfinished (if any).

Create the example workspace

☞ Click the 'Create workspace' button. In the dialog that appears, choose 'Select tutorial workspace'. Now select the 'Zinbryta initial assessment simplified' option in the dropdown and press 'add'. You should now be on the Overview screen of a fresh workspace, like on Figure 7.

🎓 The overview screen shows you the criteria and their data sources, the alternatives, and the table with measurement data.

💡 Many elements in the interface have a contextual help icon (Figure 8) that you can click for explanation and links to the relevant section in the manual.

🎓 The example concerns a simplified version of the Zinbryta assessment. The criteria are the primary endpoint (Annualised Relapse Rate) and several adverse events. Only data from the 205MS301 study are included, as can be seen in the effects table. The references column contains links to the clinicaltrials.gov registry version of this study in case you want to look at the source data.

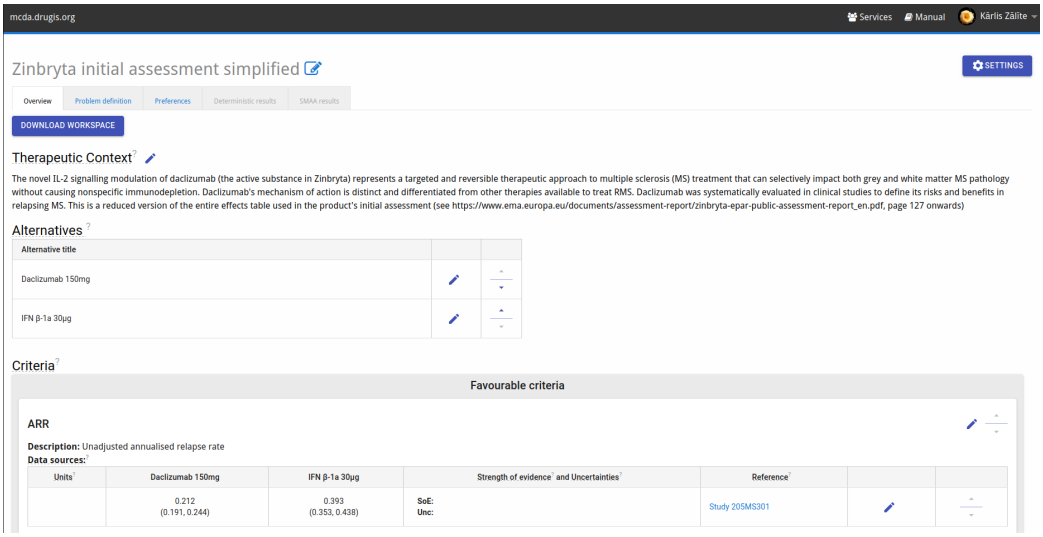


Figure 7: The overview page

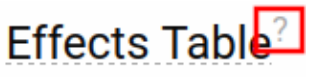


Figure 8: Contextual help icon, outlined in red

Evaluate evidence

☞ Go to the 'Problem definition' tab and take a moment to look at the effects table. Do you have a clear preference for one of the two treatments? What makes this treatment better in your view?

We are now going to quantify your preferences in several ways to see whether your intuitive answer in the previous step matches the outcome of the MCDA.

🎓 MCDA is a quantitative approach to benefit-risk assessment and ranks the evaluated treatments from least to most preferable. How preferable a treatment is, is reflected by its utility score. In ADDIS, a treatment's utility score is the sum of its per-criterion utility values. This method is called the additive value model.

🎓 Utility, as a constructed measure of well-being, has no natural scale. For simplicity, ADDIS (arbitrarily) uses the scale from 0 to 1, with 0 meaning

the worst and 1 the best possible combination of the criteria scale values.

Preferences: partial value functions

☞Go to the 'Preferences' tab.

🎓 At the top are the partial value functions, which indicate how utility changes as a function of the criteria scale values. Below this is the weights section which is the main focus of this tutorial. Before setting weights, the partial value functions need to be defined.

☞ Click on the 'Decreasing' button for ARR. Lower relapse rate is better, and we are going to assume that utility changes linearly with the relapse rate.
The range over which the partial value functions are defined depends on the data included in the effects table. These ranges can be modified in the 'Problem definition' tab, but this goes beyond the scope of this tutorial.

☞ Also define linear partial value functions for the adverse event criteria, with low values being best. The result should look like Figure 9.

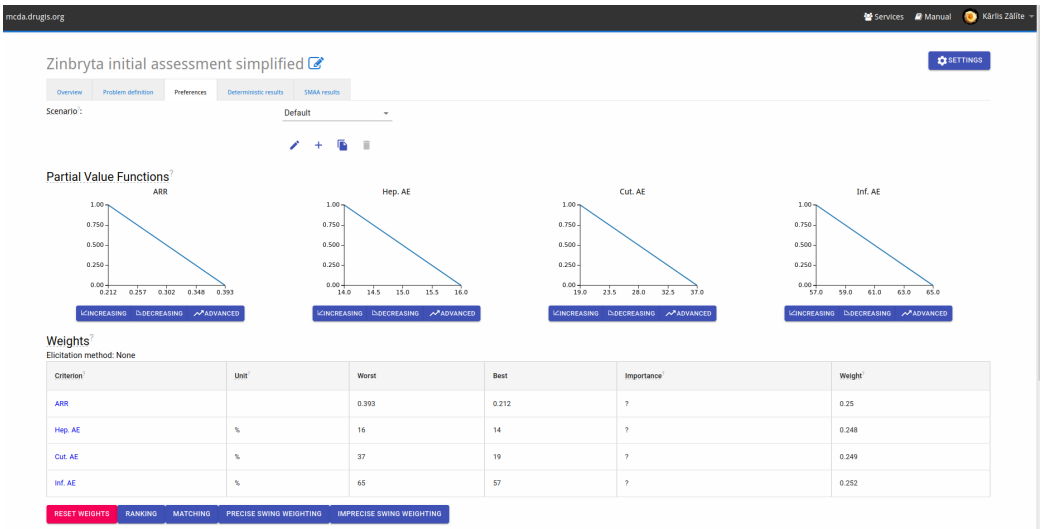


Figure 9: The preferences tab after setting the partial value functions

☞ (optional) Explore the process for defining non-linear partial value functions by clicking the 'Advanced' button under any of the functions, and adjusting the sliders. You can leave the definition process at any time by clicking on the 'Cancel' button.

🎓 Non-linear partial value functions are needed when equivalent changes on a criterion's measurement scale do not result in equivalent changes in utility. For example, one can imagine that going from severe depression to mild depression is more valuable than improving from mild to no depression (diminishing marginal utility).

Preferences: ranking elicitation

First let's see how the treatments compare if we only give an ordinal ranking, with efficacy as the most important.

☞ Click the 'Ranking' button below the weights table, then indicate that ARR is the most important criterion, followed by Hep. AE, then Inf. AE. Then click on the 'Deterministic results' tab.

🎓 The deterministic results screen shows the effects table, with values that can be changed to perform sensitivity analysis (subject of a later tutorial). Below this are the representative weights, showing which weights the system has used to calculate the value profiles. Because we did not supply direct numerical weights but did ordinal ranking instead, the system has generated a default set of weights consistent with the ranking provided. These so-called representative weights are shown in the table.

🎓 The total value indicates an alternative's overall utility according to the weights you supplied and the data in the effects table. The value profile plot below the total value table shows the contributions of each criterion to these overall utility values (Figure 10). In the current situation, we can see that Daclizumab is much better at reducing the relapse rate, while the other treatment is better as far as all the adverse events goes. Because we have indicated that ARR is much more important than the adverse events, it follows that we should prefer Daclizumab.

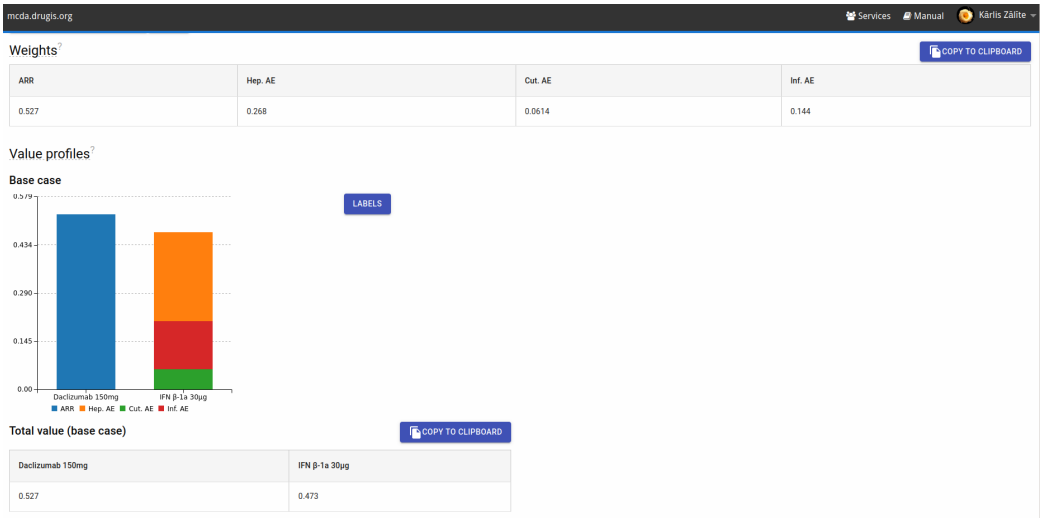


Figure 10: Deterministic analysis

Preferences: equal weights

Let's see how the picture changes if we weight all criteria equally.

☞ Go back to the 'Preferences' tab, and click the copy icon next to the scenario dropdown (Figure 11). Give the new scenario an intuitive name like 'Equal weights.'

Figure 11: Copy scenario button

🎓 Scenarios let you save different configurations of partial value functions and weights, and allow you to switch between them at will. New scenarios can be created as either a copy of the currently selected one, or completely blank, i.e. without defined partial value functions and weights.

☞ Click the 'Precise Swing weighting' button below the weights table, indicate that ARR is the most important, and then leave all the sliders at 100% and click 'Save'. Now navigate to the 'Deterministic results' tab again,

and the results should be quite different. The representative weights are 0.25 for each criterion, and IFN β-1a 30μg is now better than Daclizumab. Because there are simply more adverse event criteria, they together outweigh the higher effectiveness of Daclizumab.

💡 You can switch between scenarios using the dropdown at the top of the tab, and the results will reload.

🎓 Precise Swing weighting lets you manually and precisely set the weights of all criteria relative to the most important one, as you have just done. Leaving all weights at 100% means they are all equally important. Imprecise Swing weighting similarly lets you set the weights, but allows you to specify probable intervals for the weights, for when you are less certain about your preferences or wish to see the consequences in stochastic analysis of uncertain weights.

Preferences: matching elicitation

You can also determine your preferences by comparing alternative outcome scenarios, in the Matching elicitation process.

☞ Click the 'Matching' button under the weights table on the preferences tab. Select 'ARR' as the most important criterion in Step 1. In the following steps, you are presented with two alternative scenarios, A and B (Figure 12). Change the value for ARR in Alternative B by moving the slider until you feel that the two alternatives are approximately equal, e.g. decreasing ARR by a certain amount is 'worth' about that much increase in Hep. AE. Then click 'Next' until you have completed the elicitation. The Weights table will now have updated with the corresponding importances and weights.

☞ Go to the Deterministic results tab to see how the values of the treatments have changed. Are these results in line with your intuitive assessment at the beginning of the tutorial?
☞ After finishing filling out your preferences in the Matching elicitation, go to the Deterministic results tab to see how the values of the treatments have changed. Are these results in line with your intuitive assessment at the beginning of the tutorial?

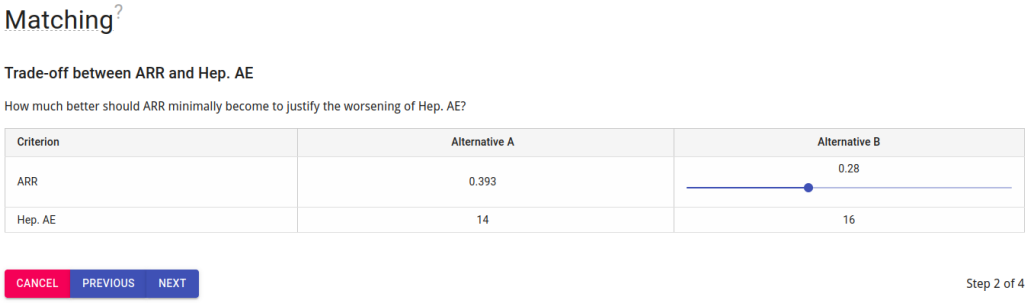


Figure 12: Matching elicitation (for one tradeoff)

Further elicitation methods (Enterprise edition)

We will here briefly cover additional elicitation methods which are only available in the enterprise edition.

☞ Go to the Preferences tab, and create a new scenario called 'Threshold' that is a copy of the 'Equal weights' scenario you created earlier. This lets you avoid having to set the PVFs again. Click the 'Threshold' button.

🎓 The Threshold technique for preference elicitation is similar to matching elicitation, with users being asked to weigh alternatives against each other based on quantitative changes in each criterion. The difference is that the user is first asked what magnitude of change in the primary criterion they find most logical to reason about.

☞ In step 1, choose 'ARR' as your reference criterion. Use an improvement by 0.05 as your reference change.

☞ In step 2 (Figure 13), adjust the changes for each other criterion so that, in your opinion, that criterion's change is approximately equivalent to an improvement of 0.05 in ARR.

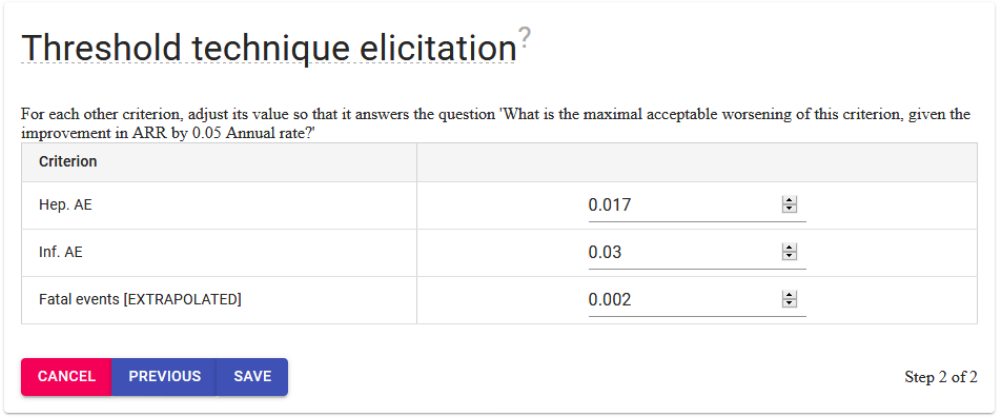


Figure 13: Threshold technique elicitation, step two: setting equivalent changes.

☞ Click 'Save' and inspect the new weights. Do they differ greatly from those you got for previous elicitation methods? Go to the 'Deterministic' tab and contrast the values of the different alternatives. Switch to one of your other scenarios and contrast the outcomes with those of your threshold weights.

☞ Go to the Preferences tab, and create a new copy of the 'Equal weights' scenario, called 'Choice-based matching'. Click the 'Choice-based matching' button.

🎓 The choice-based matching elicitation method uses an automatically-generated series of questions to approximate the user's preferences. Each question presents two alternative scenarios, and the user is asked which one they prefer. The questions are generated in such a manner that the system's uncertainty about the preferences is minimised as they are answered. This process is somewhat more labourious than adjusting a single value for each criterion, as in several other elicitation techniques. However, some users prefer being asked to judge alternatives over having to provide a numerical value directly.

☞ Answer the questions (Figure 14) as they are presented to you. Once you are done, as always contrast the generated weights and their consequences with your previous experiences.

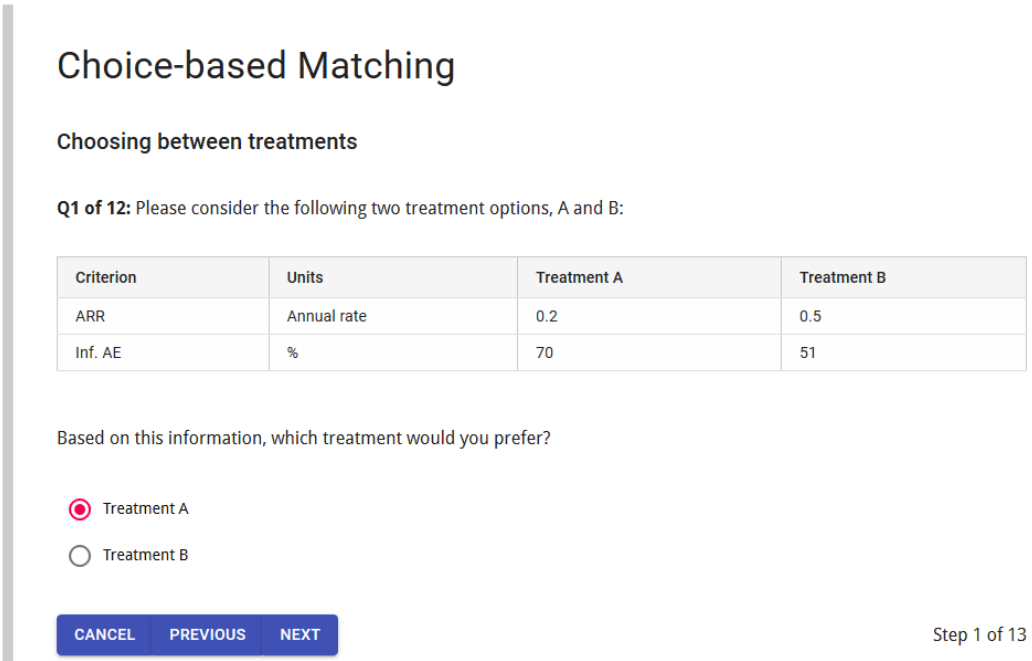


Figure 14: Choice-based matching elicitation example question, asking to judge which alternative is better.

Final words

This tutorial has demonstrated how assigning different importance to criteria can drastically change the relative value of the evaluated treatments. We've also shown how quantifying these importances makes it easy to see where these differences originate. Finally, we've shown that in the MCDA interface it is easy to input different preference scenarios with different elicitation methods, and switch between them.

Tutorial 4: sensitivity analysis

MCDA requires exact preference weights. However, in most benefit-risk assessment situations such exact weights are not available; they might lie on a range or simply be unknown. Further, the supplied data might have significant variance. In this tutorial we will investigate several ways to determine how sensitive the results of analyses are to such uncertainties.

Subjects covered

- Uncertainty in data and preferences
- Deterministic sensitivity analysis
- Stochastic sensitivity analysis

⚠ Note that this tutorial continues from the simplified version of the Zinbryta assessment used in the previous tutorial about benefit-risk analysis. At several points during this tutorial we ask you to compare results to those of the previous one, so it is helpful to have your work from the previous tutorial open in a separate browser tab or window.

Sign in to your organisation's ADDIS/MCDA.

☞ Open your browser and navigate to the URL where your organisation provides ADDIS/MCDA. Use your username and password to sign in. You will be redirected to your personal homepage, containing your previously created workspaces, both finished and unfinished (if any).

Create the example workspace

☞ Click the 'Create workspace' button. In the dialog that appears, switch to 'Select tutorial workspace' and choose the 'Zinbryta initial assessment simplified, stochastic' option. You should now be on the Overview screen of a fresh workspace. Open the settings dialog and switch the 'Measurements display mode' to ''Values used in SMAA". Note the point estimates have confidence intervals for all measurements. To see which distributions these

confidence intervals are based on, switch the measurements display to 'Entered distributions.'

🎓 For this tutorial example, we indicated explicitly when entering the data that we assume they are approximately normally distributed for their given point estimate and confidence interval (see Figure 3 in the first tutorial). This lets their distributions be used to perform stochastic sensitivity analysis, as explained towards the end of this tutorial.

☞ Click on the 'Problem definition' tab. Consider how the confidence intervals for each criterion's measurements are connected to the 'Observed Range' column in the scale ranges table.

🎓 The scale ranges for each criterion determine which highest and lowest values to consider when defining their partial value functions. Scale ranges can be wider than the observed data, but never narrower. If the data include uncertainty the confidence intervals are included in the scale ranges.

Deterministic sensitivity analysis

☞ Click on the 'Preferences' tab and define your partial value functions, as in our previous tutorial on benefit-risk analysis. Remember that lower is better for all criteria in this analysis. Note that the X-axis of each pvf corresponds to the scale range for that criterion.

☞ Perform an ordinal ranking, with ARR most important, and the AEs in decreasing importance from top to bottom. Go to the 'Deterministic results' tab, and look at the 'Value profiles' plot. Compare it to the 'Value profiles' plot of the previous tutorial's ordinal ranking scenario. Note that both alternatives derive some value from each criterion. Also note that now that uncertainty is included, Daclizumab actually has higher value.

🎓 Widening the scale ranges of your criteria is one way of incorporating uncertainty in your analyses. Since the partial value function for a criterion by definition returns an extreme value (either 0 or 1) at the minimum or maximum value of the scale range, measurements at these extremes will therefore have either maximally positive or maximally negative value. If you widen your scale ranges so that your measurements are never at these extreme ends,

they will always have some positive contribution to that alternative's value.

☞ Let's see what happens if we want to consider the case where the point estimate for ARR is too high for IFN β-1a 30μg. Click on this value in the effects table at the top of the page, and change it to approximately 0.353: the lowest value within the 95% C.I. (Figure 15). Click the 'Recalculate value profiles' button below the effects table, and take a look at the new results. As it turns out, this single change is not sufficient to change the benefit-risk balance.

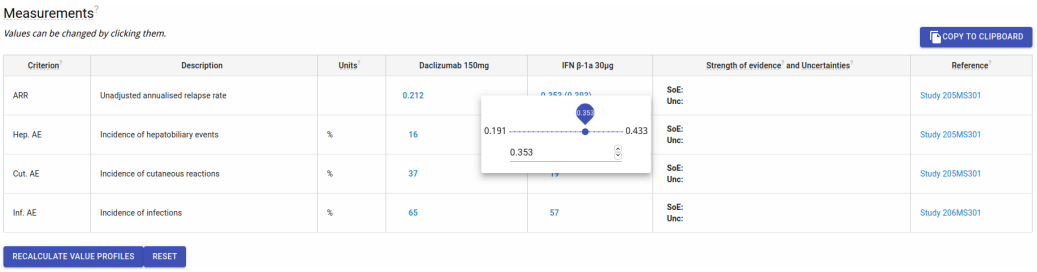


Figure 15: Changing the effect value

☞ Scroll down to the bottom of the page and take a look at the plots in the 'One-way sensitivity analysis' section. These give some insight into what the consequences of changing a single value would be. In the left ('Measurements') plot select IFN β-1a 30μg as the alternative and observe the changes. Pay particular attention to the intersection point of the two lines.

🎓 The measurements plot of the one-way sensitivity analysis shows you how the total value of a criterion changes if you change its measurement for a specific alternative, while keeping all other values constant. In other words, we could have predicted that the change we made in the previous step (to 0.353) would not be sufficient to upset the benefit-risk balance, because the intersection point with the Daclizumab is only at approximately 0.314. The measurements plot thus lets you explore the sensitivity of the benefit-risk balance to each individual effect. Note that for linear pvfs this is rather straightforward, but nonlinear ones make it more interesting.

🎓 Similarly, the 'Preferences' plots let you see how the value of all alter-

natives changes with the weight of a specific criterion. Note that, since all weights should always sum to 1, this means that the weights of the other criteria also change implicitly. Instead of their value, their proportional share of the remaining weight is kept constant.

🎓 Deterministic analysis lets you easily predict the results of a single change, and check the consequences of different measurement data. However, it would be extremely labour-intensive to manually make a lot of changes and aggregate the results into an overview of the possibilities given the measurements, your preferences, and their uncertainties. This need is addressed by stochastic multicriteria acceptability analysis (SMAA) which we'll briefly discuss in the next section.

Stochastic sensitivity analysis

☞ Go to the 'SMAA results' tab. Take a moment to look at the outputs. Most important are the rank acceptability plot and table at the top of the page (Figure 16). These indicate how frequently each alternative had a specific rank in the different configurations of measurements and preferences that were generated.

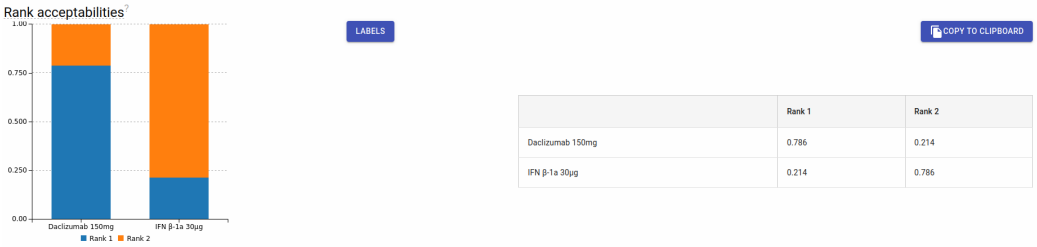


Figure 16: Rank acceptabilities

🎓 SMAA models explore uncertainties in the measurements and preferences by systematically varying their values[1]. The set of variations (of which there can be hundreds of thousands) can be analysed in several ways. We here use the rank acceptability: for each variation the alternatives are ranked according to their calculated value, and then the proportion of variations in

which an alternative had each specific rank is reported.

☞ Go to the 'Preferences' tab, create a new scenario called '100-75-50-25'. Set the partial value functions as before, and use Precise Swing to set the Criteria weights as: ARR 100%, Hep. AE 75%, Cut. AE 50% and Inf. AE 25%. Go to the 'Deterministic results' tab, and you should see that the value of both alternatives is approximately equal. Now navigate to the 'SMAA' tab and observe the results. You should see that each alternative is ranked as best in roughly 50% of all cases. This is consistent with the deterministic analysis, where the value for both alternatives is approximately equal.

☞ Switch to your workspace from the previous tutorial. Create a scenario in the Preferences tab called 'ranked weights', then use Precise swing to specify the weights as: ARR 100%, Hep. AE 50%, Cut. AE 25% and Inf. AE 12%. This results in a representative weight distribution approximately equal to the one automatically generated for deterministic analysis of the case where the criteria are ranked.

☞ Go to the 'Deterministic results' tab and use the scenario switching to go back and forth between the 'ranked weights' scenario and the 'Default' one (assuming you kept that scenario as using ranking; otherwise do a new ranking elicitation). The results and representative weights should be similar.

☞ Switch to the 'SMAA results' tab and again switch back and forth between the two scenarios. Now you should see a great difference. For the specific weight distribution we picked, there is no uncertainty in either the measurements or the preferences, and thus all scenarios result in the same ranking. However, in the 'Default' scenario where only ranks are specified, the different ways in which the weights can be distributed while preserving their ranking are taken into account, showing that for only approximately half such rankings Daclizumab 150mg is better than IFN β-1a 30μg.

🎓 Uncertainty can also lie in the preferences. If only a ranking is specified, there are infinitely many ways to pick the actual weight values for the criteria that still satisfy the given ranking. SMAA also varies the preferences if there

[1]SMAA samples from probabilistic distributions for these values - for a more in-depth explanation of the process, see the MCDA manual and Tervonen & Lahdelma (2007)

is uncertainty there.

Final words

This tutorial showed how to explore potential consequences of uncertainty in your measurements and preferences for the benefit-risk balance. It also demonstrated how to determine the sensitivity of the benefit-risk balance to changes in measurements and preferences. Finally, we've shown how to interpret the output of SMAA models and their bird's eye view of what is possible.

Tutorial 5: Workspace rights management (Enterprise edition)

Subjects covered

- Managing other users' rights on your workspaces
- Changing the owner of a workspace

Prerequisites

This tutorial assumes some familiarity with the ADDIS/MCDA interface, and also assumes that there is at least one other user registered in the system.

User rights

💡 In ADDIS/MCDA, a user can have the following rights for a given workspace:

- Owner: can edit the workspace, and manage who has access.
- Editor: can edit the workspace.
- Reader: can view the workspace.

By default, users can only view and edit their own workspaces. They can grant access to others explicitly using the rights administration interface.

Getting started

☞ Open your browser and navigate to your MCDA server, and sign in. ☞ Create a new workspace for the tutorial by clicking the 'Create workspace' button and choosing any example workspace.

List of workspaces

💡 On your personal home page in MCDA, workspaces are sorted by your access rights to them. There are three categories:

- Workspaces you own
- Workspaces you can work on (but are not owned by you)
- Workspaces you can view

As an example, see Figure 17. If any of the categories is empty, it will not be shown on the page.

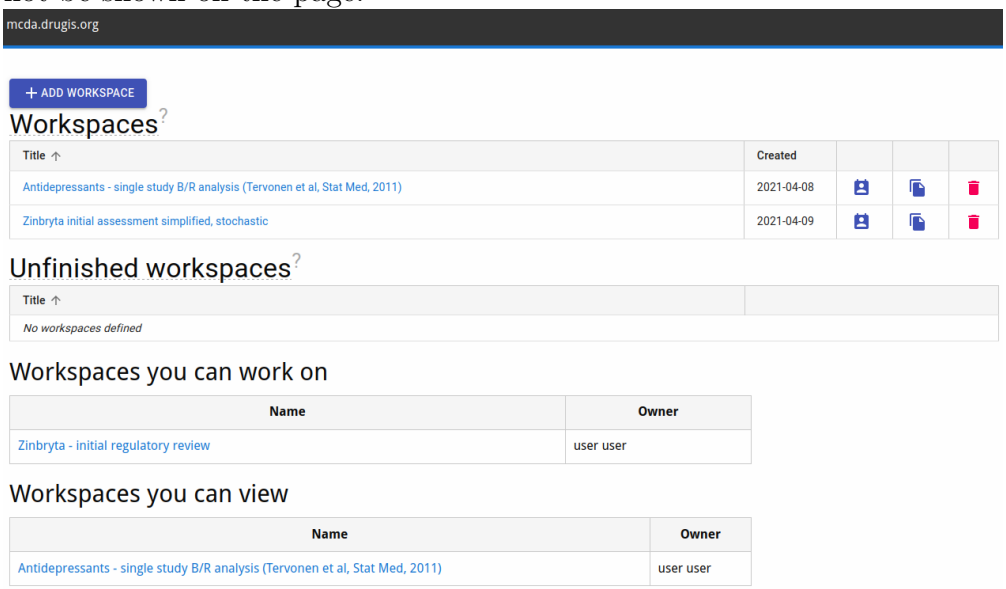


Figure 17: Workspaces organized in lists.

Manage user rights

You will notice that you have several actions available in the list of workspaces that you own. ☞ Either from your home page, of from the view of your example workspace, click on the 'Manage user rights' button. This takes you to the user rights management screen. You can grant other users Editor or Reader rights using the dropdown menus. Once you are satisfied

with your changes, click the 'Save rights' button. ⚠This tutorial cannot predict your environment and tell you who to grant which rights to. Choose a colleague you know, or ask the systems administrator to create an extra testing account. ☞ Besides granting others access, you can also remove rights by clicking the 'Delete' button in the 'Users with rights on this analysis' list. Afterwards, click the 'Save rights' button.

Changing the owner of a workspace

⚠Note that this process is irreversible except by the new owner, or by the administator. ☞ Click on the 'Change owner' button. Select a user from the drop down list. This user will be granted ownership of the workspace. Your rights will be set as 'Editor'.

Tutorial 6: Survey creation and response analysis (Enterprise edition)

Subjects covered

- Creating a survey
- Customising and publishing a survey
- Analysing survey responses

Prerequisites

This tutorial assumes some familiarity with the ADDIS/MCDA interface, either from following previous tutorials or independent study.

ADDIS MCDA surveys

ADDIS/MCDA can be used to elicit personal preferences and explore their consequences for the benefit/risk balance of a given problem. However, in many situations one might be more interested in the preferences of a larger group of people, e.g. a group of regulators or the patient population for a disease. ADDIS/MCDA lets you create and distribute surveys to such groups simply by sharing a hyperlink. Users following this link will have their preferences elicited, and their response will be made available for aggregate-level analysis. This tutorial guides you through the process of creating and publishing a survey, as well as the subsequent analysis of survey responses.

Getting started

☞ Open your browser and navigate to your MCDA server, and sign in.

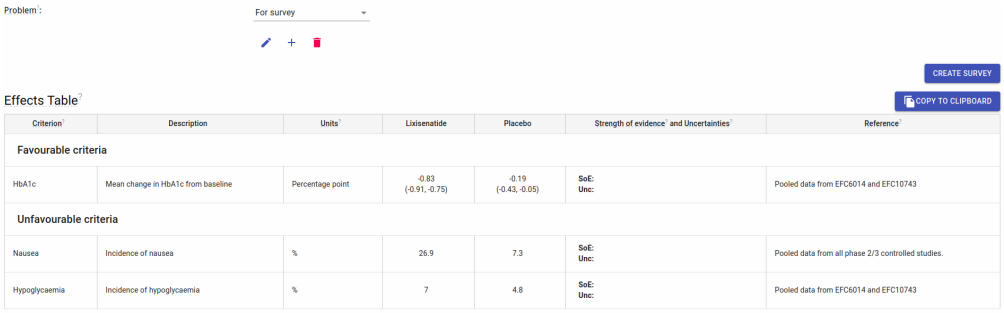
☞ Create a new workspace for the tutorial by clicking the 'Create workspace' button and choosing the 'Lixisenatide simplified' option from

the tutorial workspaces.

Creating the survey

☞ Navigate to the 'Problem definition' tab. Note that the 'Create survey' button is disabled. Hovering your mouse over the button will inform you that there are missing or empty values in your problem table, which you can verify in the effects table shown. Since it would be redundant to create surveys based on problems which cannot be analysed, this is not possible in the system.

☞ Create a new subproblem called 'For survey' without empty cells and with only a single data source per criterion. We recommend deselecting Exenatide, and using the pooled data source for this example, as in Figure 18.



Criterion	Description	Units	Lixisenatide	Placebo	Strength of evidence and Uncertainties	Reference
Favourable criteria						
HbA1c	Mean change in HbA1c from baseline	Percentage point	-0.83 (-0.91, -0.75)	-0.19 (-0.43, -0.05)	SoE: Unc:	Pooled data from EFC6014 and EFC10743
Unfavourable criteria						
Nausea	Incidence of nausea	%	26.9	7.3	SoE: Unc:	Pooled data from all phase 2/3 controlled studies.
Hypoglycaemia	Incidence of hypoglycaemia	%	7	4.8	SoE: Unc:	Pooled data from EFC6014 and EFC10743

Figure 18: Simplified effects table for lixisenatide, ready to be used as basis for a survey.

☞ Note that the 'Create survey' button is now enabled. Click it, take a moment to read the question and click 'Yes'. The dialog will close and you will be redirected to the newly created survey.

💡 For simplicity's sake, each problem in ADDIS/MCDA can currently have precisely one survey based on it. Should you want to create multiple surveys based on the same problem table for any reason, create a new problem from the base problem and create a new survey for the new problem.

Modifying and publishing the survey

☞ Take a look at your new survey. Note that the ADDIS/MCDA survey tool is separated into tabs, which are intended to guide you through the process of editing and publishing the study, progressing from left to right. The first ('Problem') tab shows you the effects table of the problem it is based on, and the scale ranges and units of the effects (Figure 19).

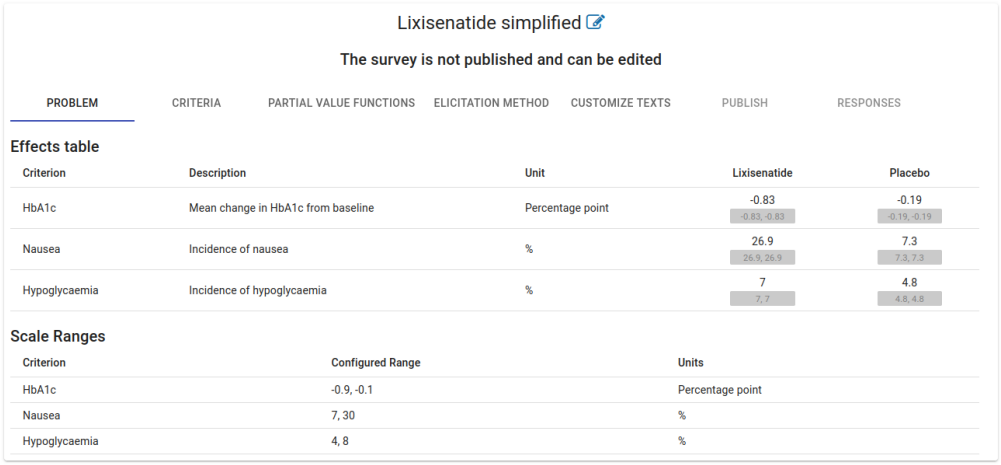


Figure 19: Welcome screen of the survey tool, showing the effects table the survey is based on.

☞ Click on the 'Criteria' tab. Here you can edit the name, description and unit of measurement for the criteria. If your survey is intended for laypeople you might for example want to edit 'HbA1c' to be called 'Blood sugar level change.'

⚠ Editing the unit of measurement here is purely cosmetic and will not affect any functionality besides labelling. It is your responsibility to not e.g. give a criterion the unit '%' which reports non-percentage values.

☞ Click on the 'Partial value functions' tab. Here you set the direction of the partial value functions for the criteria, i.e. whether lower values are better than higher ones or vice versa. In this example, we wish for lower blood sugar levels as well as fewer incidences of nausea and hypoglycemia, so all partial value functions should be set to 'lower.'

💡 The main ADDIS/MCDA application lets you define more complex non-linear partial-value functions, but we have omitted this option here for simplicity's sake.

☞ Click on the 'Elicitation Method' tab. Here you choose the method that will be used to elicit the responders' preferences. The same options are supported here as in the main ADDIS/MCDA application. For most users we recommend the 'Choice based matching' method which asks a series of questions requiring the responder to choose between scenarios. For this tutorial however, please select the 'Matching' option.

☞ Adjust the test slider for one of the criteria, then change the step size and adjust the slider again. Note the difference in behaviour. During matching, the surveyee will be asked to adjust a value so that two alternative scenarios are equivalent. Setting the step size here will determine the minimum adjustment size they can make. Choose a step size for each criterion that feels appropriate to you given the scale range (meaning the range of possible values for that criterion).

☞ Click on the 'Customize texts' tab. Here you can customise several of the texts that will be shown to the responders during the survey. Note that the 'Default' button in each text editor will always return the text to the simple defaults first shown here.

💡 The 'Question during matching elicitation' text has several phrases in all capitals. These are template values, which will be substituted by the appropriate text or value during the survey. These templates are covered in more detail in the following 'test run' section of this tutorial. Several other elicitation methods also let you use templates in the accompanying texts.

☞ Make any preliminary text changes that you wish, and then click the 'Test run' button. This will let you run through a demonstration of what a responder will encounter during your survey. Note the two round buttons at the bottom, which allow you to edit texts in place and stop the test run, respectively (Fig. 20).

Figure 20: Edit text (left) and stop test run (right) buttons.

☞ On the welcome screen in the test run, click the edit button (pencil icon). A dialog will open similar to the one on the Customize texts tab. Note that the criteria names have been replaced by so-called template texts, surrounded by '%' symbols. Click the question mark button in the editor's toolbar to the right of the 'Default' button to show a legend with the available template texts. Use this knowledge to extend the question with information about the current worst value, e.g. 'It is currently X' where X is the worst value of criterion 1. Click the 'Save' button and note the effect of this change. See Fig. 21

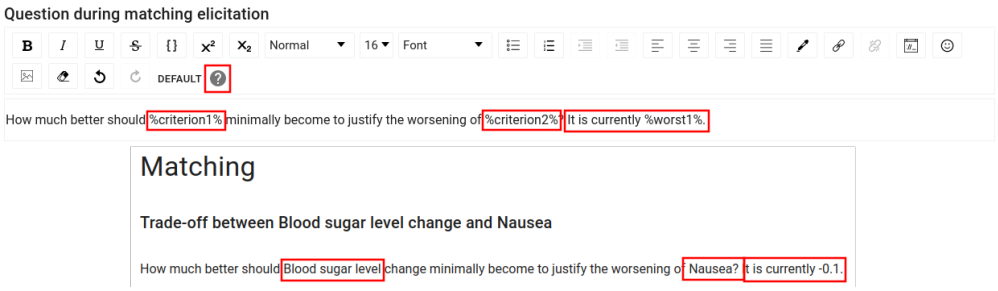


Figure 21: Modifying a question with templates, during and after editing. Note the explanation text which is toggled using the '?' button. Templates are substituted by their corresponding values when shown to the surveyee.

☞ Make any further changes you wish and continue your test run. Any changes you made have been saved, as you will see after ending the test run.

☞ Enter any text as your identifier, and proceed. Select the most important criterion, and proceed again. Now you are presented with a matching trade-off scenario.

☞ Proceed through the elicitation process until the final screen. Note that again you can edit this text.

☞ Assuming that the test run proceeded to your satisfaction, you are now ready to publish your survey. Proceed to the 'Publish' tab and click the 'Publish survey' button. This is also where you can close the survey for responses once its projected running time has ended. After publishing your survey, it will be available to anyone at the displayed URL.

💡 If you are logged into the ADDIS/MCDA system, going to a survey URL that you own will let you manage it as you have been doing. Other users will see only the elicitation survey, as you will verify in the next step.

Collecting and analysing survey responses

☞ Open a new private browser window and go to the survey URL. You should be presented with the welcome screen as you configured it.

☞ We need some completed surveys for the next step, so in this new window complete the survey at least three times, with different preferences.

☞ Close the private window and return to the main survey interface. Click on the 'Responses' tab, and you should see the responses you provided in a table, with an overview of their preferences (Fig. 22)

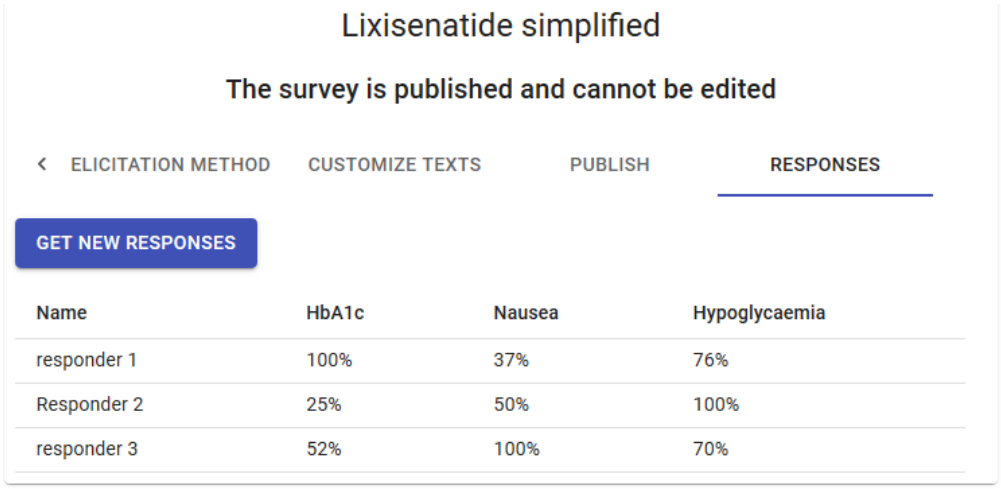


Figure 22: The survey response table.

☞ Return to the main ADDIS/MCDA application, and refresh the page. The 'Survey results' tab should now be available if you have selected the problem for which you created the survey. Click on this tab.

🎓 The ADDIS/MCDA survey response analysis is based on our SMAA (Stochastic Multicriteria Acceptability Analysis) interface, but instead of sampling stochastically from the possibility space of the constraints given by the measurements and preferences, each survey response is treated as a sample. Therefore, the rank acceptabilities now show the distribution of preferences in the surveyed population, i.e. which proportion of the population would assign each rank to each alternative. Similarly, the weights shown for each criterion are sampled from distributions which are constrained by the survey responses.

☞ Take a moment to examine the interface. We assume you are already familiar with the SMAA tab. The main difference here is the 'Survey responses' table which shows an overview of which responses are included in the analysis, similar to the responses tab in the survey tool. Note the distribution of the rank acceptabilities, and see whether you can deduce which responses are responsible for which ranks.

☞ Click the + button next to the selected 'Everything' aggregated anal-

ysis at the top of the page (Fig. 23). Add a new aggregated analysis where you have excluded at least one of your scenario responses.

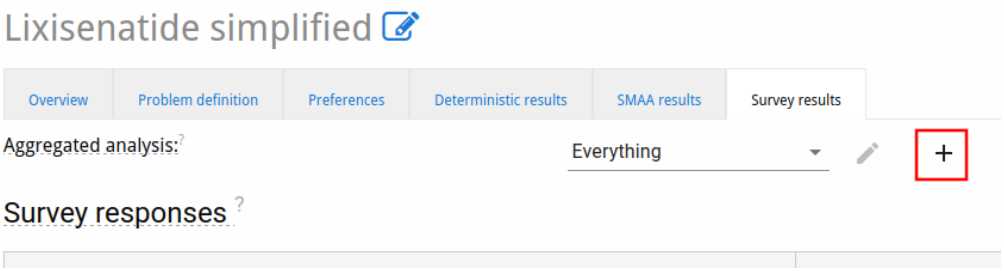


Figure 23: Survey analysis creation button.

☞ Switch back and forth between the automatically-generated 'Everything' aggregated analysis and the new reduced one you just created, and note any differences. Can you explain them based on the excluded survey response?

Final words

This tutorial showed how to create durveys starting from an analysable effects table. It also demonstrated how to customise the survey, and preview the consequences of any changes. Finally, it showed how to obtain an overview of the survey responses and analyse them in ADDIS/MCDA.