Eliciting Prior Opinion on External Biases

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In order to capture expert opinion for the epilepsy example presented in Wadsworth et al. (Under review) we developed an interactive web application written in R (R Core Team, 2015) using the Shiny package (Chang et al., 2017). We illustrate the proposed scheme with an application to anti-epileptic drug (AED) development, see Girgis et al. (2010) and Nedelman et al. (2007). The following contains screen shots from the app in order to illustrate how our elicitation scheme should be performed. The elicitation scheme is called by the function `elicit_func`. This function has only has one argument (`OUT_dir`) specifying the directory generated files are to be saved to.

Motivating example

Suppose exposure-response (E-R) data are available from H historical trials of adjunctive topiramate which recruited both adults and adolescents. Let Y_{ij} represent the response of subject i in historical study j, for $i = 1, \ldots, N_j$, and $j = 1, \ldots, H$, where $Y = \log\{Z + 110\}$, with Z the percent change from baseline in seizure frequency. For our example, we assume that Y is normally distributed and that a linear model is an adequate description of the underlying relationship between exposure and response. Dropping the i and j subscripts for clarity, let A be a binary indicator of age which takes the value 1 for adolescents and 0 otherwise. Let

$$Y = \gamma_0 + \gamma_C C + \gamma_A A + \gamma_I CA + \epsilon,$$

where C represents the steady state trough concentration under repeated dosing and $\epsilon \sim N(0, \sigma^2)$ is a random error term. The relationship between exposure and the expected PD response is said to be identical in adults and adolescents in each study if $\gamma_A = \gamma_I = 0$.

Consider now the data that we would accumulate if we performed an E-R study, indexed by T, in adults and younger children. Suppose we measure PD responses Y_{iT}, for $i = 1, \ldots, N_T$. Again, dropping subscript i for clarity, let

$$Y_T = \beta_0 + \beta_C C_T + \beta_A A_T + \beta_I C_T A_T + \epsilon_T,$$

where $\epsilon_T \sim N(0, \sigma^2)$; C_T is a measure of exposure defined similar to C; and A_T is a binary age covariate taking the value 1 for younger children and 0 otherwise. E-R relationships in adults and younger children would be said to be identical if $\beta_A = \beta_I = 0$. We relate parameters in the source and target populations described by the above models via the relations:

$$\beta_A = \gamma_A + \delta_A \qquad \text{and} \qquad \beta_I = \gamma_I + \delta_I.$$

Here and represent external biases arising because E-R curves in adolescents and younger children may differ. It is these δ_A and δ_I parameters we want to elicit expert opinion on.

δ_A δ_I

Inferring bias priors

Obviously, these δ_A and δ_I parameters are challenging to elicit directly, so instead we propose having experts, conditional on the existing adult and adolescent data, provide their opinion on E-R relationships in younger children. We assume that prior opinion on the vector of bias parameters can be modelled as a bivariate normal distribution, written as $\underline{\delta} \sim N_2(\underline{\nu}, \Pi)$, where $\underline{\nu} = (\nu_A, \nu_I)$ are the prior modal values of the biases.

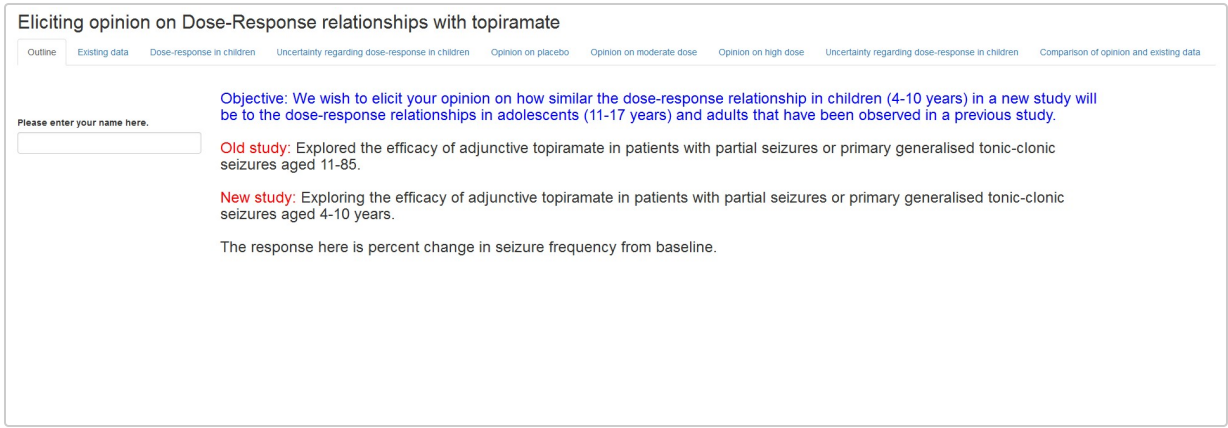
By asking an expert for their best guesses at the average PD responses in children on placebo and a `high' dose, we deduce fitted values of ν_A and ν_I . To find ν_A , one can subtract $(\gamma_0 + \gamma_A)$ from the expert's best guess at the average response on placebo; ν_I is obtained by subtracting $(\gamma_C + \gamma_I)$ from the slope calculated by dividing the difference between the expert's best guesses at the expected PD responses on a high dose and placebo by the high dose level.

An expert's uncertainty about the average PD response in younger children on a dose $d^\star$ is established by asking questions to establish the 5 th, 25 th, 75 th and 95 th percentiles of their prior distribution for this quantity. Given values of ν_A and ν_I , we can then adapt the approach of Neuenschwander et al. (2008) to search over configurations of Π to find the triplet which defines a positive definite variance matrix and minimises the absolute difference between percentiles of the fitted prior and the expert's stated percentiles. To ensure positive definiteness, Π is represented in the optimisation routine using the Cholesky decomposition.

Our protocol for eliciting $\underline{\nu}$ and Π is described in the following section.

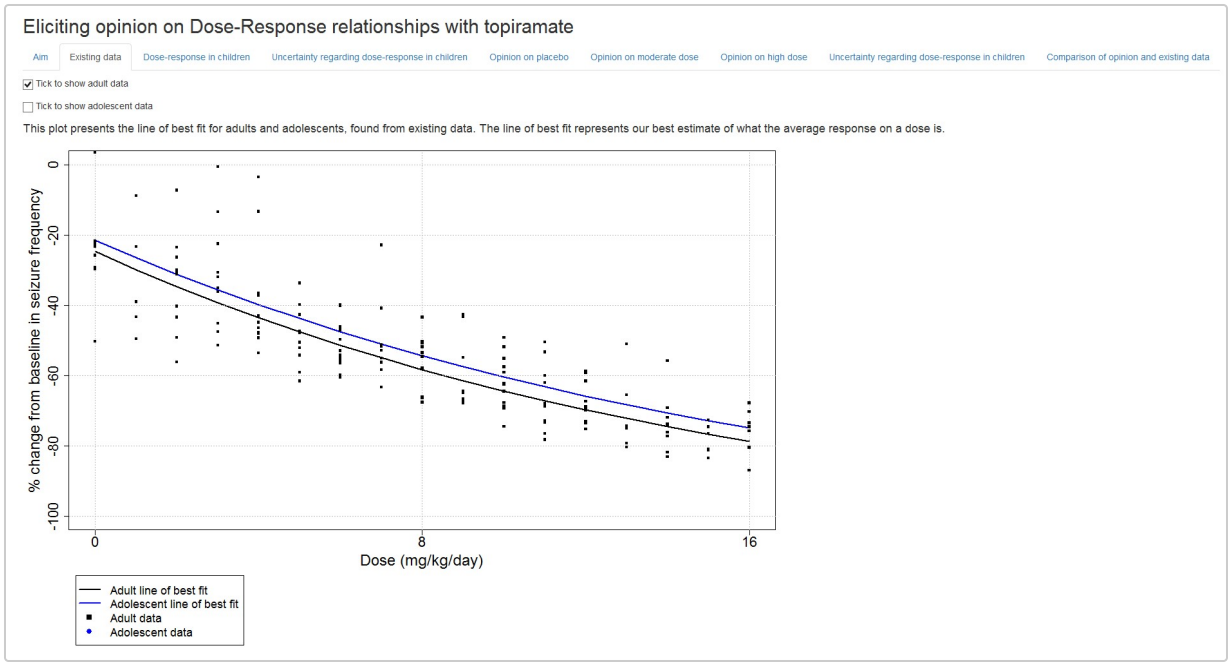
Elicitation scheme

The app expects the statistical facilitator to summarise the protocols of the historical trials (eligibility criteria, outcomes, treatments, etc.) and present this to the experts. The following gives a brief version of this used for our example:



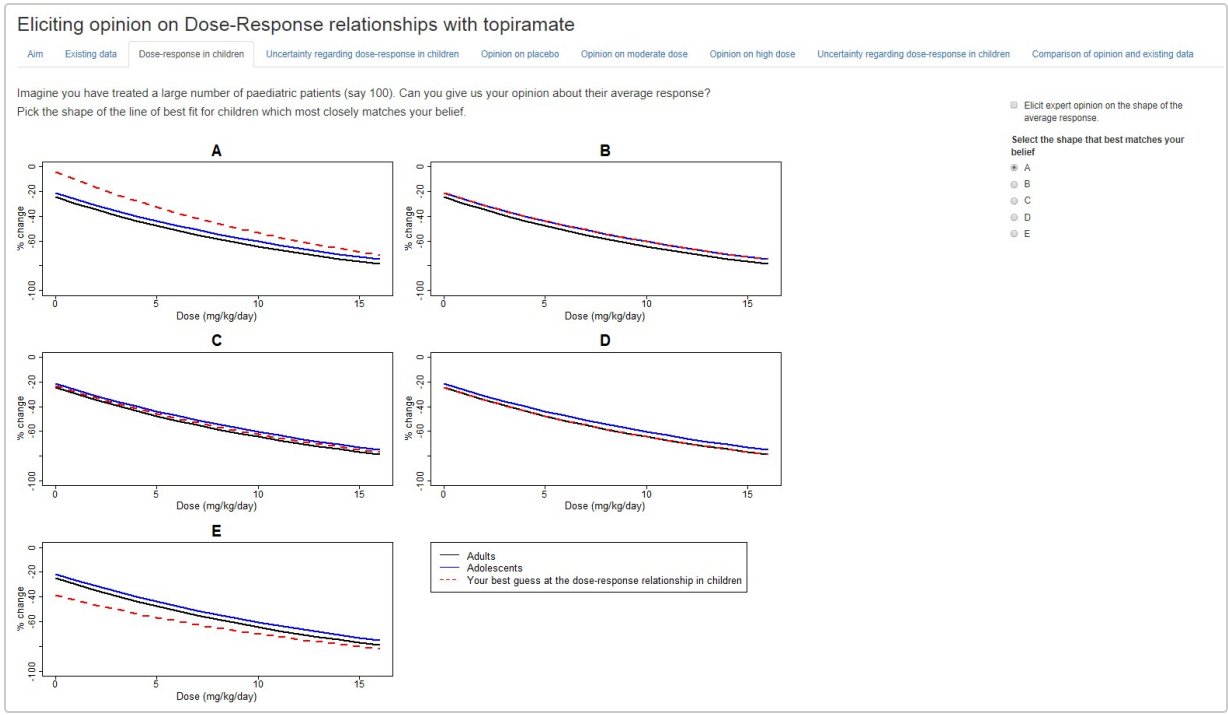
Following this, the statistical facilitator then directs the experts through the following eliciation protocol:

Step 1 Display the fitted dose-response curves for adults and adolescents derived from the historical data. If individual patient data (IPD) are available, overlay these as a scatter plot to provide a more complete description of the existing data, as illustrated here:

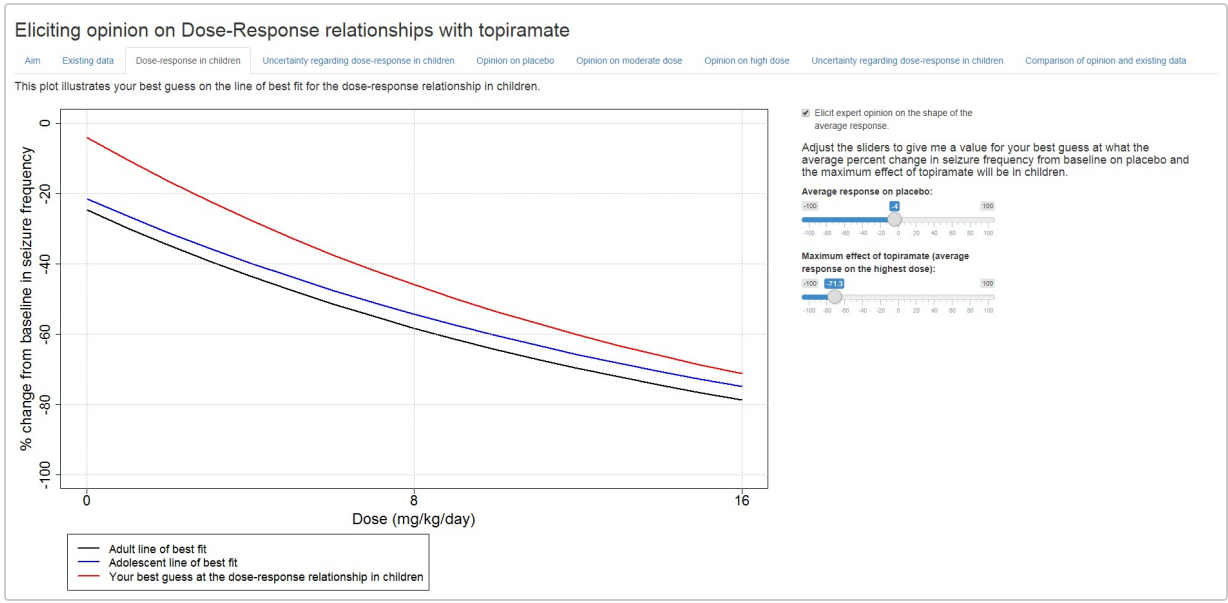


Conditional on these existing data, elicit opinion on how the average PD response in younger children varies with dose according to Steps 2-5. When interacting with clinicians, the dose-response curve should be referred to throughout as the line of best fit that would be plotted if we were able to randomise a large number of younger children to each of a range of dose levels.

Step 2 To elicit the expert's prior modal guess at the dose-response curve in younger children given existing data, first show them a range of different shapes for the dose-response curve in this age group and ask them to select the one which most closely reflects their current best guess, as shown here:

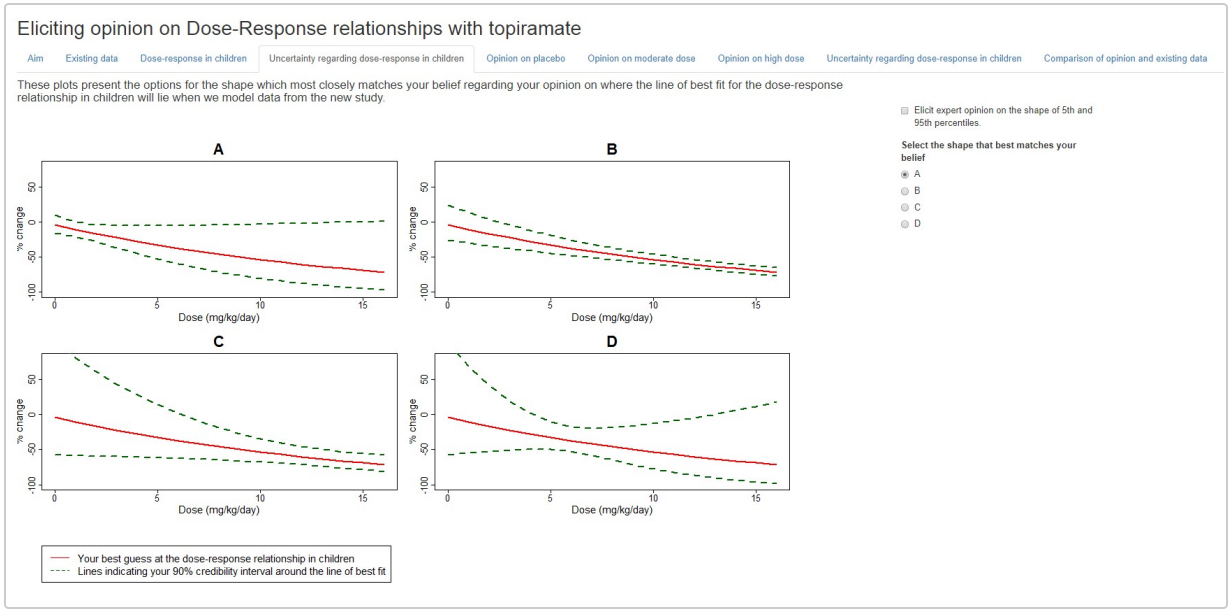


The range of shapes should include curves which: a) lie above the fitted adult curve; b) between the fitted adult and adolescent curves; c) lie below the fitted adolescent curve; d) are identical to either the fitted adult or adolescent curves. Guide the expert to iteratively refine their selected shape until they find a line which more closely reflects their current best guess at the dose-response curve in younger children, as illustrated here:

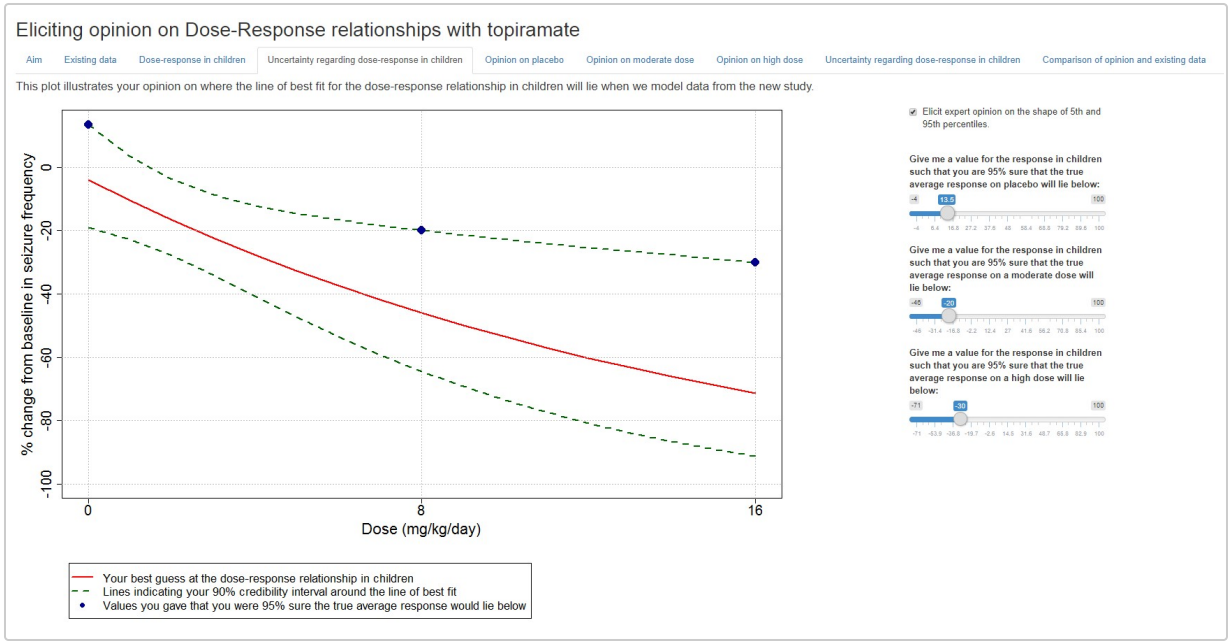


Refinements are driven by the expert's answer to the following question, which is repeated for placebo and dose d_H : "Given the existing data, give your best guess at the average response amongst children aged 2-11 years on dose d of the test treatment". From this step of the elicitation process, the prior modal values, $\underline{\nu}$, of the bias parameters δ_A and δ_I can be deduced.

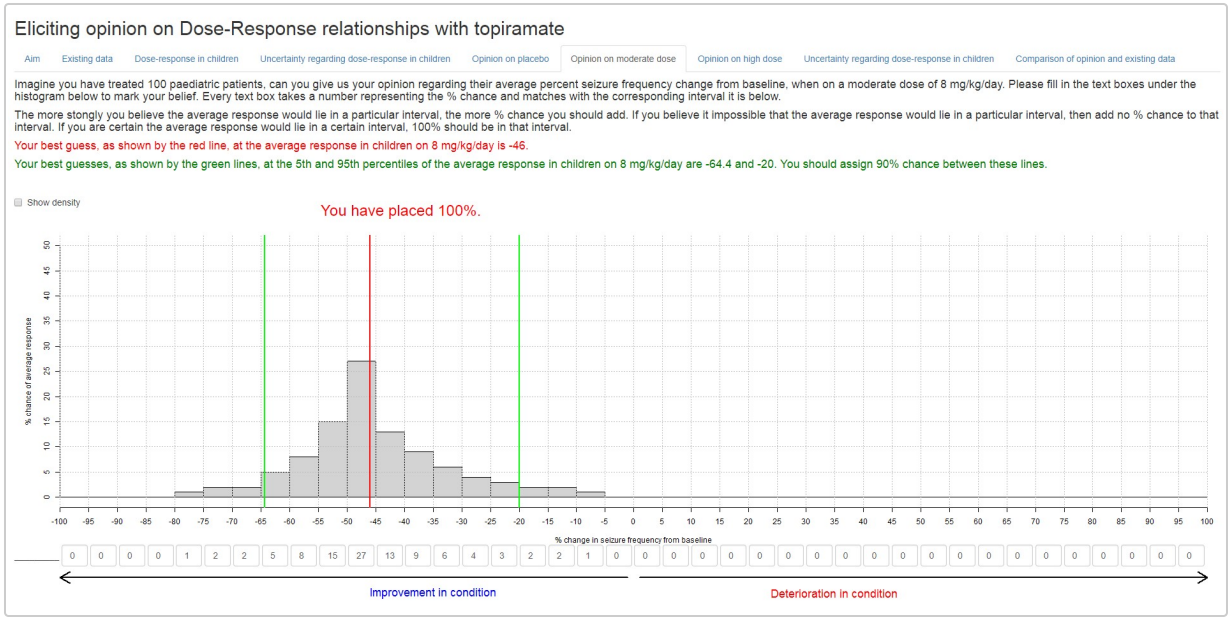
Step 3 To establish the expert's uncertainty about the dose-response relationship in younger children, given the existing data in adults and adolescents, explain the concept of a credibility interval. Then show the expert a range of shapes which might be formed by interpolating between the limits of their 90% credibility intervals for the average PD response in younger children on placebo and doses d_M and d_H . Four options are shown here:



These options have been informed by discussions with clinical experts. The statistical facilitator should interpret each shape and ask the expert to select the one most closely describing their prior uncertainty. For each dose in turn, the expert is then asked: “Given the existing data, state a value which you are 95% sure the average response amongst younger children on dose d of the test treatment will lie below”. The expert’s answer is the 95th percentile of their prior distribution for the expected PD response at the dose in question. Only the upper limits of credibility intervals need to be elicited to deduce fitted values for elements of the variance-covariance matrix of $\underline{\delta}$ (due to symmetry). Despite this, the fitted upper and lower limits of credibility intervals for expected PD responses are shown to the expert. This stage of the elicitation procedure is illustrated here:



Step 4 To further refine and validate the expert's priors, elicit three histograms representing their prior distributions for the average PD response of younger children on placebo, dose d_M and dose d_H . This information is collected to check the consistency of the expert's opinion, to increase the stability of the prior fitting routine (by also using the 25th and 75th percentiles) and to provide a more accurate quantification of the expert's opinion. Each histogram is elicited by asking the expert to allocate a prior weight to different response intervals, where their weights must sum to 1. For reference, coloured lines marking the mode and 95th percentiles elicited from Steps 2 and 3 are shown, along with the 5th percentile implied by symmetry. This process is shown here:



The elicited histograms provide the 5th, 25th, 75th and 95th percentiles of the expert's prior distributions for the average PD response of younger children on placebo, dose d_M and dose d_H , which can be used to allow parameters of the prior variance matrix of $\underline{\delta}$ to be established.

Step 5 Once all three histograms have been elicited, feed back to the expert summaries of the prior distribution for the dose-response relationship in younger children that would be implied by their expressed opinions. In particular, allow the expert to compare the credibility bound established from Step 3 with that from Step 4, to ensure that they are confident the histograms reflect their belief. The average response line will be that given in Step 2, whilst the uncertainty around that line will be taken from the opinions elicited in Step 4. If the fitted prior lacks face validity, the expert should be allowed to re-evaluate their answers to Step 4 until they feel confident that their beliefs have been adequately captured. The following two figures illustrate this step of the process:

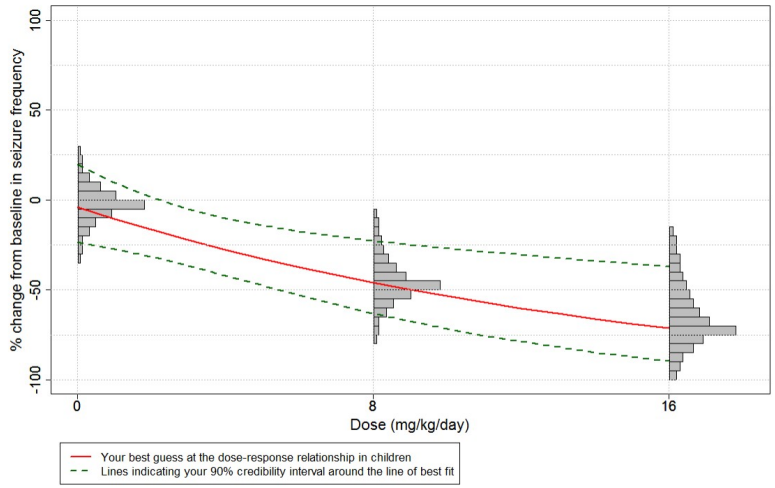
Eliciting opinion on Dose-Response relationships with topiramate

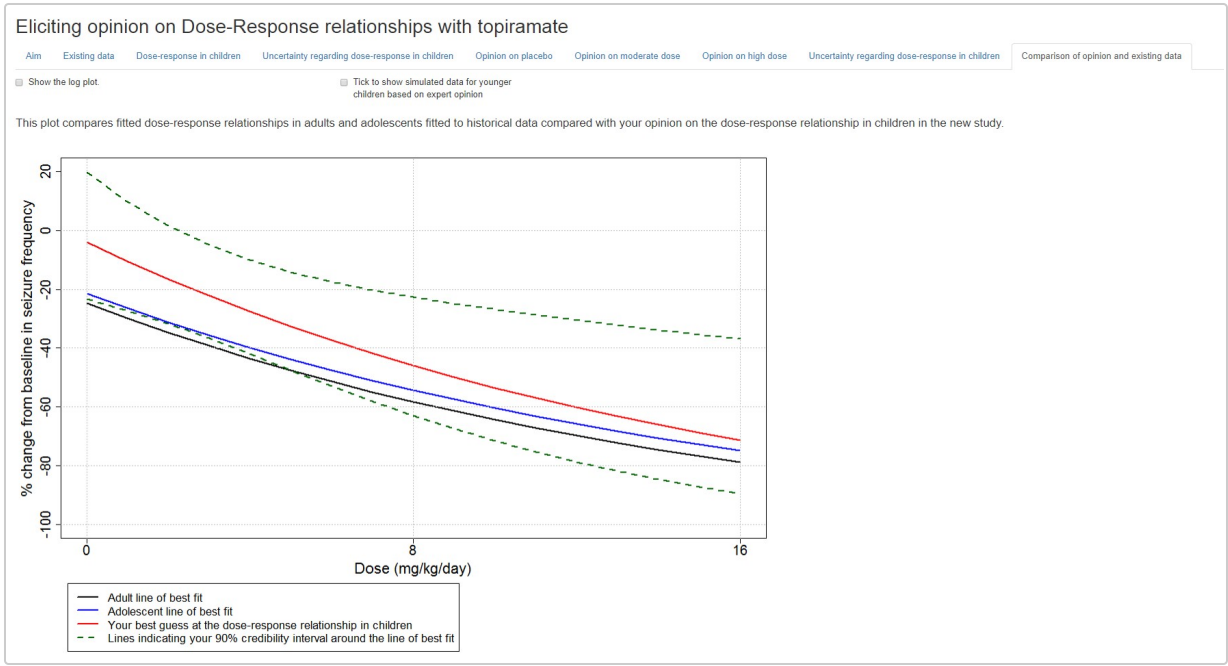
Aim | Existing data | Dose-response in children | Uncertainty regarding dose-response in children | Opinion on placebo | Opinion on moderate dose | Opinion on high dose | Uncertainty regarding dose-response in children | Comparison of opinion and existing data

☑ Tick to show uncertainty ☐ Show uncertainty from earlier shape choice

☑ Show histograms. ☐ Show densities.

This plot illustrates your opinion on where the line of best fit for the dose-response relationship in children will lie when we model data from the new study.





Following the completion of the scheme and all final plots being displayed to the expert, a range of plots and the fitted values of the bias prior will be saved to `OUT_dir`.

References

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