Borrowing information across patient subgroups in clinical trials, with application to a paediatric trial: Additional material

Derivations for formulae (4) and (5)

Using only the data from the target subgroup, we would estimate the treatment effect θ_1 in the target subgroup as follows:

$$\theta_1|y_1 \sim N(y_1, \sigma_1^2)$$

Using only the data from the larger subgroup, we would estimate θ_1 as follows:

$$\theta_1|y_0, \delta \sim N\left(y_0, \sigma_0^2+\sigma_\delta^2\right)$$

The joint likelihood function is then:

$$L(\theta_1; y_1, y_0, \delta) = \frac{1}{\sigma_1^2} exp\left\{\frac{(y_1-\theta_1)^2}{2\sigma_1^2}\right\} \frac{1}{\sigma_0^2+\sigma_\delta^2} exp\left\{\frac{(y_0-\theta_1)^2}{2\left(\sigma_0^2+\sigma_\delta^2\right)}\right\}$$

By differentiating the log likelihood and setting to 0, it can be shown that the maximum likelihood estimator of θ_1 is:

$$\widehat{\theta_1} = \frac{y_1/\sigma_1^2 + y_0/\left(\sigma_0^2+\sigma_\delta^2\right)}{1/\sigma_1^2 + 1/\left(\sigma_0^2+\sigma_\delta^2\right)}$$

with the following variance:

$$Var\left(\widehat{\theta_1}\right) = \frac{1}{1/\sigma_1^2 + 1/\left(\sigma_0^2+\sigma_\delta^2\right)}$$

We have assumed a vague normal prior for θ_0: $\theta_0 \sim N(0, 10^6)$, and have assumed $\delta \sim N\left(0, \sigma_\delta^2\right)$ where σ_δ^2 is assumed fixed and known. The implied prior for $\theta_1 = \theta_0 + \delta$ is normal with zero mean and very large variance and therefore the posterior mean and variance approximate the likelihood-based estimate and variance. The posterior distribution for θ_1 is therefore (equation (4) in main text):

$$\theta_1|y_1, y_0, \delta \sim N\left(\frac{y_1/\sigma_1^2 + y_0/\left(\sigma_0^2+\sigma_\delta^2\right)}{1/\sigma_1^2 + 1/\left(\sigma_0^2+\sigma_\delta^2\right)}, \frac{1}{1/\sigma_1^2 + 1/\left(\sigma_0^2+\sigma_\delta^2\right)}\right)$$

The posterior mean is a weighted average of the estimated treatment effects y_1 and y_0 obtained for the target subgroup and larger subgroup respectively. We observe that the relative weight given to the larger subgroup is (equation (5) in main text):

$$\frac{1}{\sigma_0^2+\sigma_\delta^2} \Big/ \left(\frac{1}{\sigma_1^2} + \frac{1}{\sigma_0^2+\sigma_\delta^2}\right)$$

Full mathematical model (as presented descriptively in the main text)

$y_1 \sim N(\theta_1, \sigma_1^2)$, $y_0 \sim N(\theta_0, \sigma_0^2)$ where σ_1^2 and σ_0^2 are assumed fixed and known (estimated from data)

$\theta_1 = \theta_0 + \delta$, $\theta_0 \sim N(0, 10^6)$, $\delta \sim N\left(0, \sigma_\delta^2\right)$ where σ_δ^2 is assumed fixed and known (informed by elicited opinion)

$$\theta_1 | y_1, y_0, \delta \sim N\left(\frac{y_1/\sigma_1^2 + y_0/\left(\sigma_0^2 + \sigma_\delta^2\right)}{1/\sigma_1^2 + 1/\left(\sigma_0^2 + \sigma_\delta^2\right)}, \frac{1}{1/\sigma_1^2 + 1/\left(\sigma_0^2 + \sigma_\delta^2\right)}\right)$$

Materials used to support elicitations

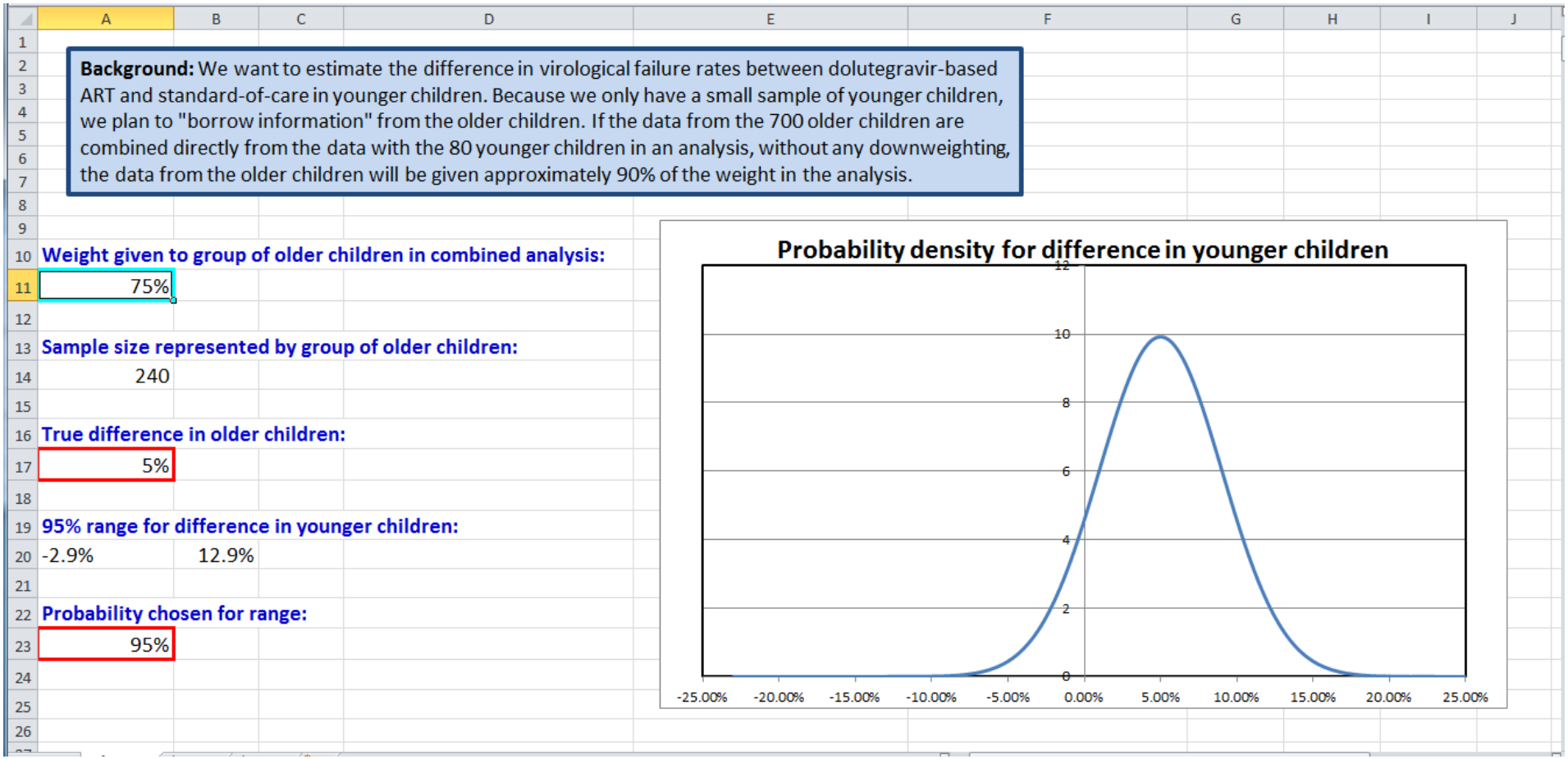

Figure S1 Excel spreadsheet illustrating the correspondence between weights allocated to the data from older children and beliefs about the uncertainty range for the treatment difference in younger children. Choices for the weight (blue cell), assumed treatment difference in older children, and the level of uncertainty assigned to the range (red cells) could be altered within the spreadsheet. In the spreadsheet, treatment differences were expressed as % benefit in favour of DTG to facilitate communication during elicitations, because it's easier to discuss changes to positive rather than negative values. (In the remainder of the paper, however, the sign is reversed and treatment differences are expressed as DTG – SOC.)

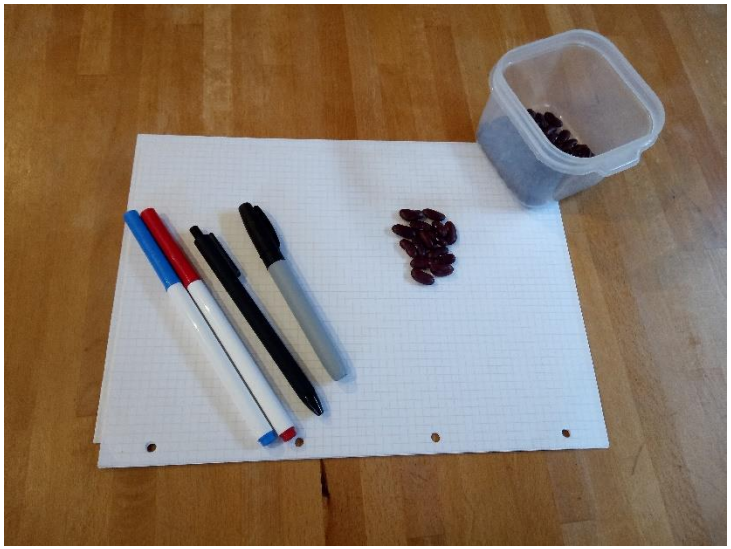

Figure S2 Drawing materials and counters provided to help experts visualise their probability beliefs.

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