

Analysing small groups within clinical trials, while borrowing information from larger groups

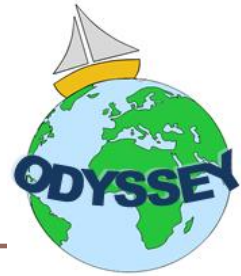
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Background

Problem: how to analyse a small distinct group of patients within a clinical trial?

- Sample size is small, so a stand-alone analysis of these patients lacks power
- We plan to borrow information from a larger patient group (or multiple groups) within the same trial
- Clinical opinion can be sought on differences between patient groups, to determine how much information should be borrowed



- Randomised trial of dolutegravir (DTG)-based antiretroviral therapy (ART) vs. standard of care (SOC) in children with HIV infection
- Children recruited are starting first-line ART or switching to second-line ART
- Trial includes 700 children aged <18 years weighing 14kg or more, and 80 children weighing 3-14kg
- Non-inferiority trial

Problem: children weighing 3-14kg were recruited 12 months later and need to be analysed separately

Analysis of the younger children

We want to estimate the difference in treatment failure rates by 96 weeks between dolutegravir-based ART and standard-of-care in younger children (weighing <14kg).

One option is to use the data from the younger children in a stand-alone analysis.

Another option is to assume the treatment difference is identical in older and younger children, and combine the two data sets in a pooled analysis.

Choosing how to weight the analysis

If data from older and younger children are combined directly, the older children receive 90% of the weight.

This would be appropriate if the treatment difference is believed to be identical in the two cohorts.

Choosing weights

- We could instead “downweight” the data from older children in the pooled analysis.
- Choice of weights can be based on how similar the treatment difference is believed to be in the two cohorts.
- Clinical opinion is needed to inform us how we should make use of the data from the older children.

Model for difference between younger and older children

We want to estimate the difference θ_1 in clinical/virological failure rates in the younger (<14kg) children.

Data from younger children provide an estimate of θ_1 :

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

Data from older children provide an estimate of θ_0 :

$$y_0 \sim N(\theta_0, \sigma_0^2)$$

We use a parameter δ to describe the relationship between treatment differences in younger and older children:

$$\theta_1 = \theta_0 + \delta$$

Weighting in Bayesian analysis

Clinical opinion can provide an informative prior distribution for the difference: $\delta \sim N(0, \sigma_\delta^2)$

Based on clinical opinion, the weighting given to the data from the older children in the combined analysis is altered, by adding to the sampling variability.

Relative weight given to the data from the older children:

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

Collecting clinical opinions

Opinions were obtained from 13 clinical experts.

Given an assumed treatment difference of 5% in older children, we asked about their expectations for the treatment difference in younger children.

We asked for upper and lower limits for likely values:

“What size of treatment difference in younger children would surprise you?”

We then elicited how much probability they would assign to this range.

Feedback on impact of opinions

Next, clinical experts were asked to choose a relative weight to assign to the data from older children.

Feedback was provided using a spreadsheet showing the correspondence between relative weights and uncertainty ranges for the difference in younger children.

They were asked to choose a final answer, based on considering both weights and uncertainty ranges.

Spreadsheet used to provide feedback

Background: We want to estimate the difference in virological failure rates between dolutegravir-based ART and standard-of-care in younger children. Because we only have a small sample of younger children, we plan to "borrow information" from the older children. If the data from the 700 older children are combined directly from the data with the 80 younger children in an analysis, without any downweighting, the data from the older children will be given approximately 90% of the weight in the analysis.

Weight given to group of older children in combined analysis:

75%

Sample size represented by group of older children:

240

True difference in older children:

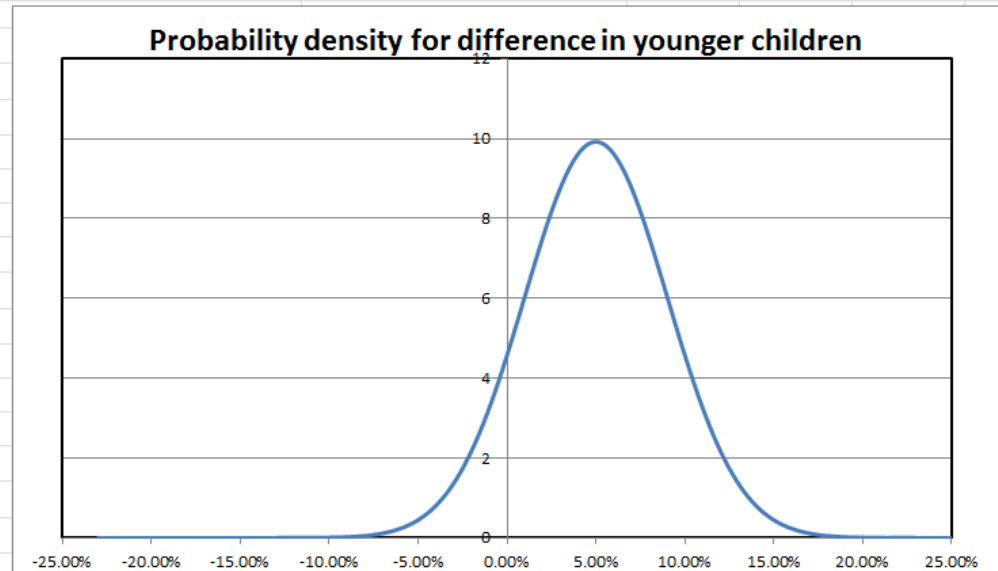
5%

95% range for difference in younger children:

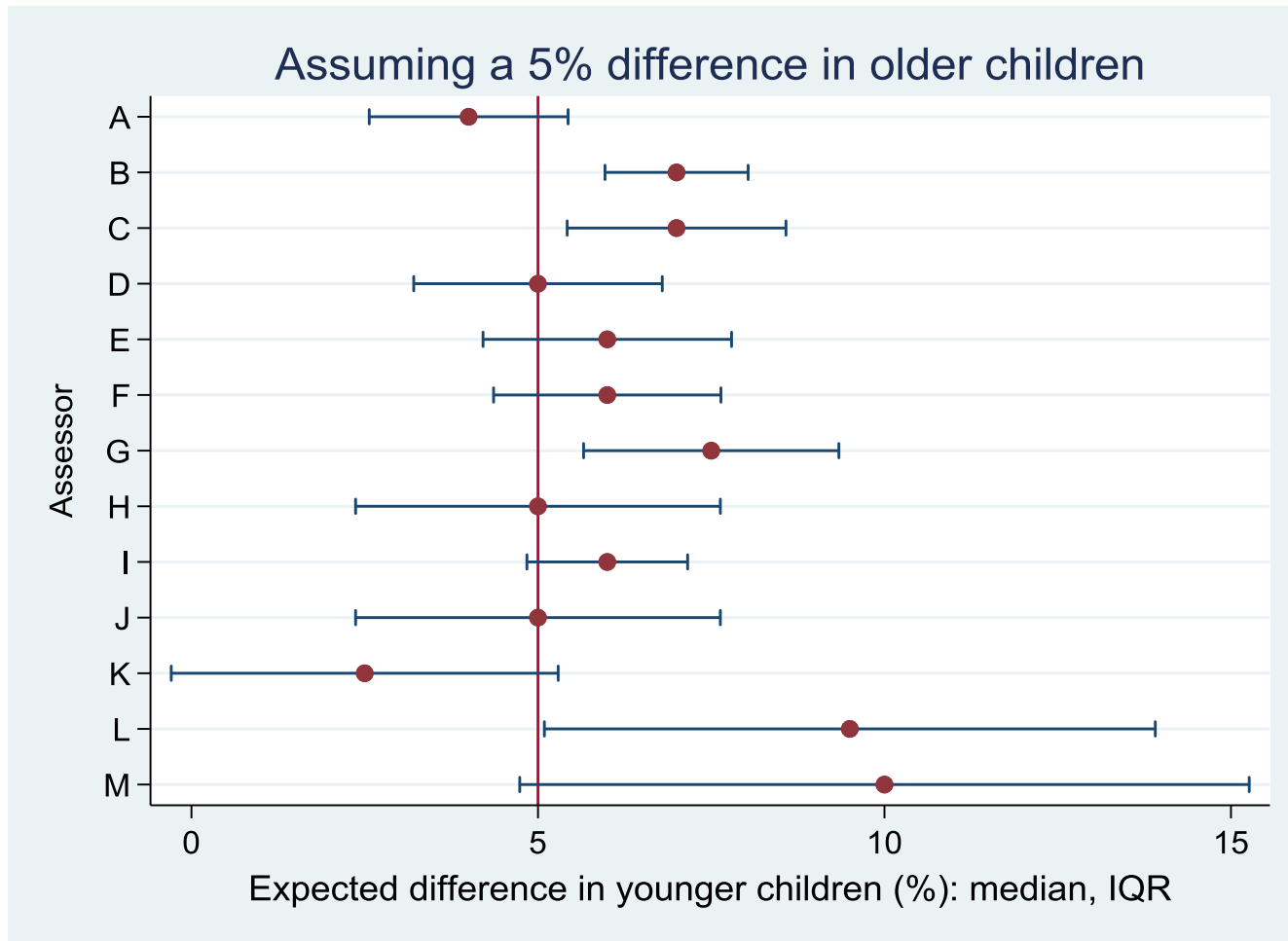
-2.9% 12.9%

Probability chosen for range:

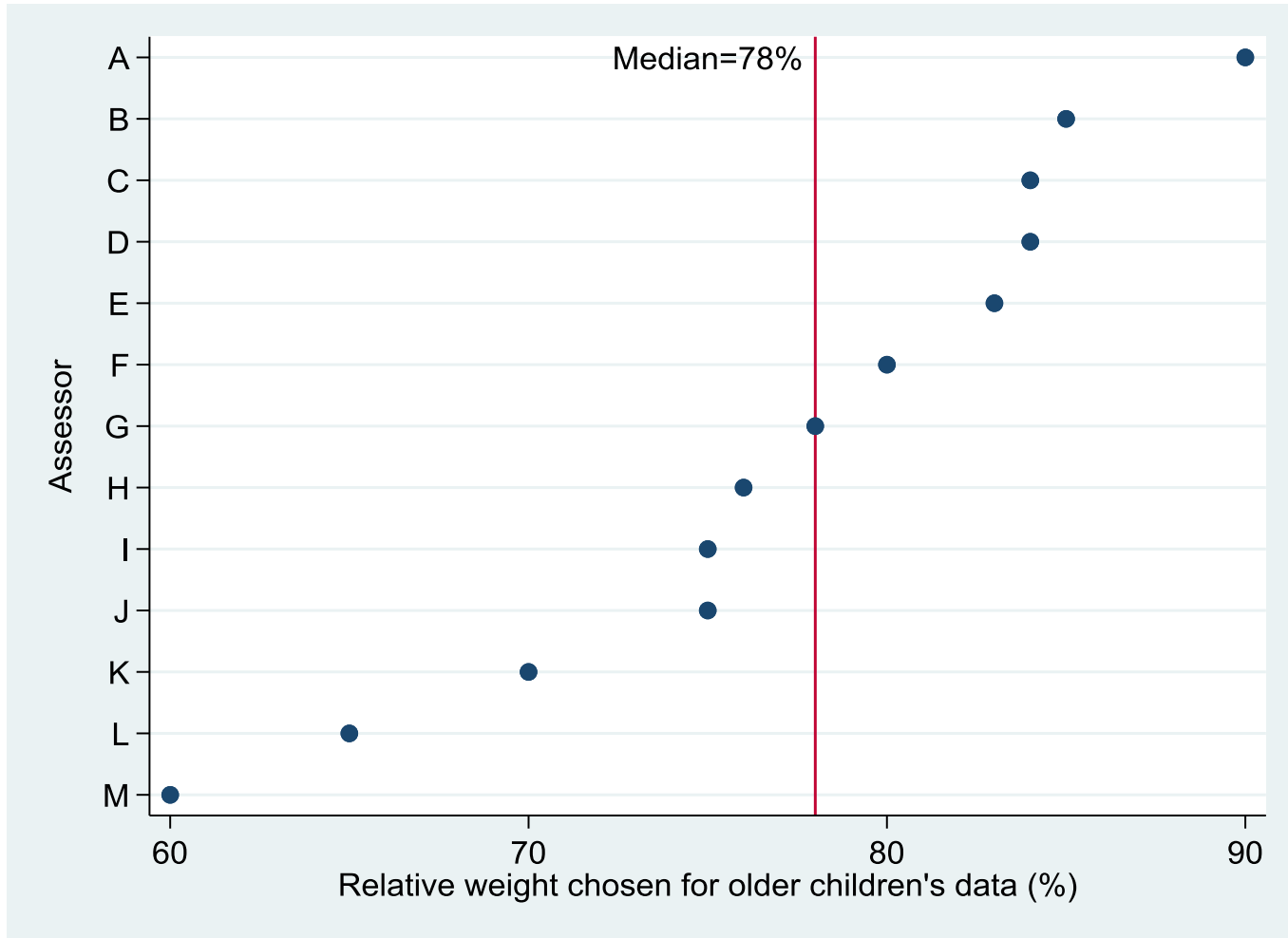
95%



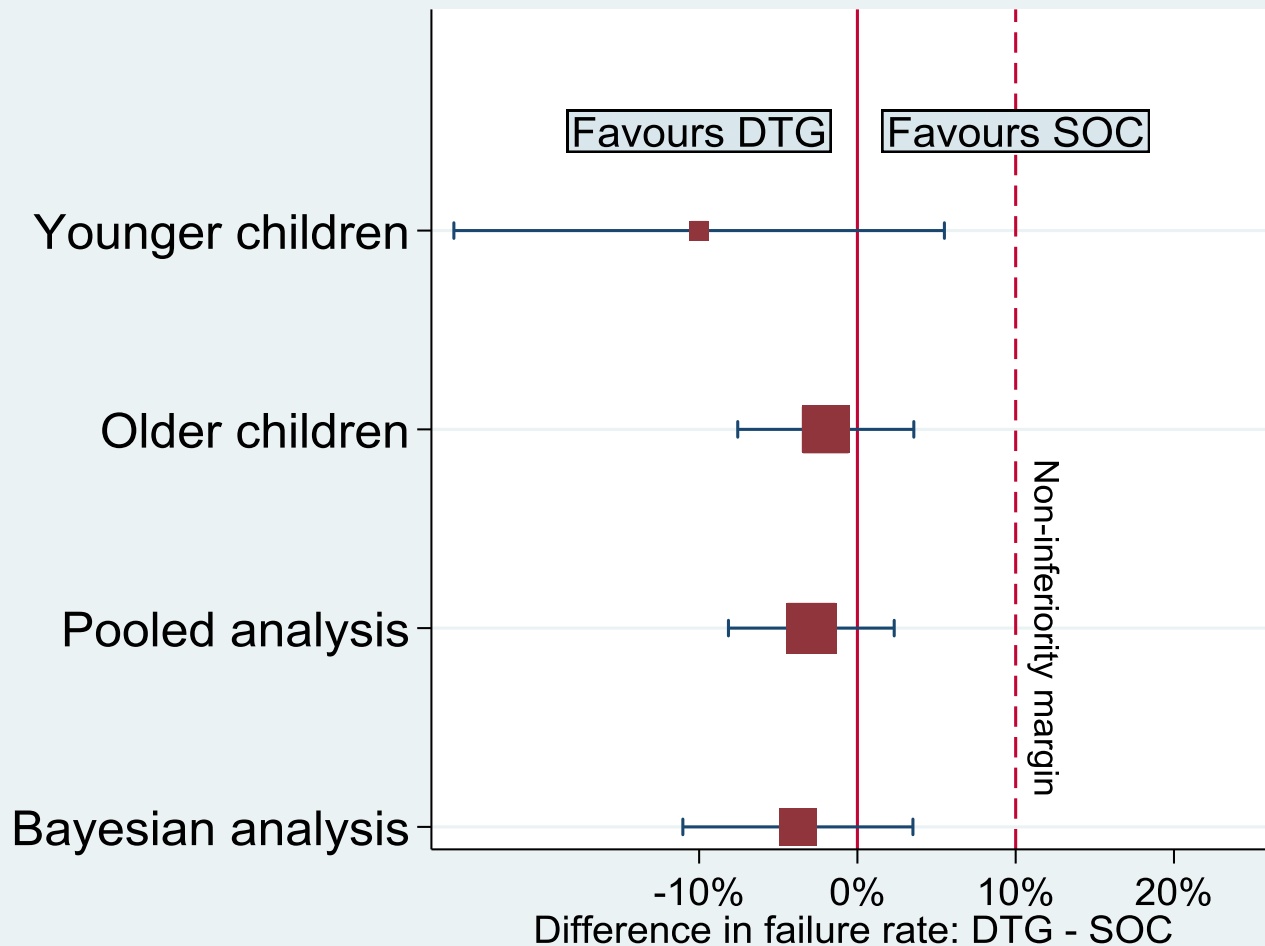
Elicitation results: uncertainty ranges



Elicitation results: relative weights chosen

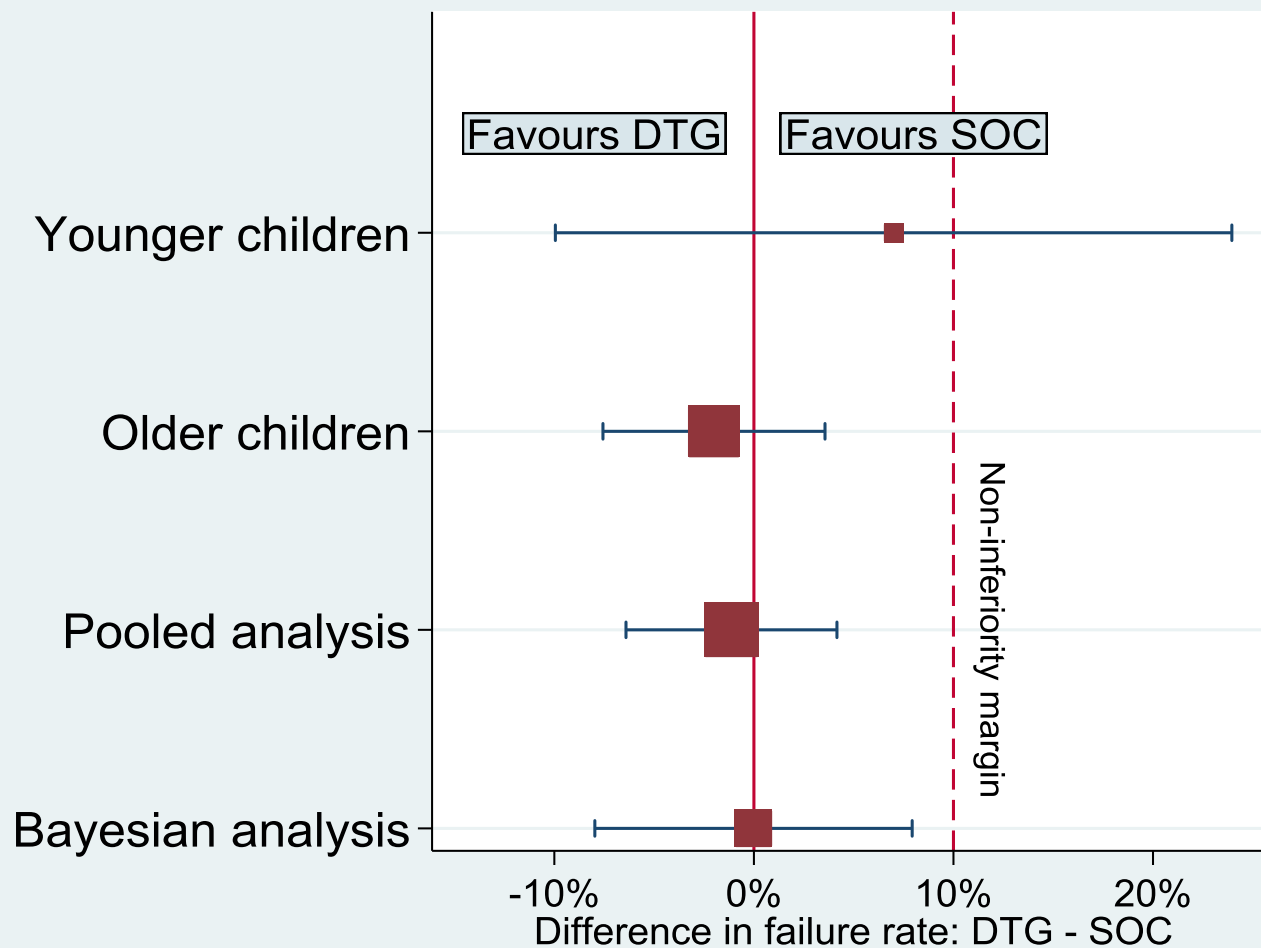


Example 1: more extreme estimate in younger children



Bayesian analysis:
78% weight given
to older children

Example 2: direction of estimate differs in younger and older children



Bayesian analysis:
78% weight given
to older children

Summary of results

- The Bayesian analysis will be the primary analysis of the younger children, in which data from the older children will contribute 78% of the weight
- The data from the 700 older children will be downweighted to an effective sample size of 284
- The effective total sample size in the Bayesian analysis of the younger children will be 364
- A stand-alone analysis of the younger children and an unweighted pooled analysis will be reported alongside the Bayesian analysis

Designing a basket trial with small baskets

Basket trials in oncology study cancers which are linked biologically, regardless of site of cancer in the body.

Proposed trial in squamous cell cancers

- Mucosal squamous cell cancers have a shared phenotype and clinical similarities across sites
- Planning to recruit across six different cancer sites
- Sample sizes in two sites (cervical, head and neck) will be high and provide adequate power for stand-alone analyses
- Sample sizes in four additional sites (anal, vulval, vaginal, penile) will be low because the cancers are less common

Borrowing information across cancer sites

- Idea: borrow information for the small baskets (rare cancer sites) from the large baskets (common cancer sites)
- Degree of borrowing will be based on prior distributions describing likely variation of treatment effects across sites
- Prior distributions could be informed by external data where available (studies of similar interventions) or opinion (clinical experts) or a combination of both
- Offers benefits over excluding rare sites from the trial (no opportunity to learn about them) or analysing rare sites separately (very low power)

Discussion

- Borrowing information from larger groups can facilitate estimation in small patient groups, providing gains in power and precision
- Areas of application include paediatric populations and rare diseases
- Degree of borrowing cannot be informed by the trial data alone, unless there are a moderate number of groups with well estimated treatment effects
- In some settings, external evidence about differences between groups could be obtained from comparable previous studies

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