STATISTICS AND STATISTICAL SOFTWARE

Meta-analyses were performed with R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria: www.R-project.org) [1] and the meta [2], tidyr [3], and ggplot2 [4] packages in RStudio, version 1.1.463 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA: http://www.rstudio.com/) [5]. In a meta-analysis, the sample size of each study and the between-studies heterogeneity influence the weight of the study on the pooled estimate. Because of expected heterogeneity between the populations of different studies (for example, in age, etiology, neurodevelopment, etc.), we considered a priori a random-effects model. This a priori choice was supported by the results of between-study heterogeneity as measured by the I^2 index [6].

Publication bias is a type of systematic error that occurs when studies are selectively published based on their results. Typically, studies with large effect sizes or statistically significant differences are more likely to be published [7]. When publication bias occurs, the published set of data may not be a representative sample of reality. A meta-analysis always yields a mathematically accurate synthesis of the studies included in the meta-analysis [7]. However, if the available studies are not an accurate representation of reality because some studies are published and others are not, the meta-analysis results may suffer from this publication bias [7]. To retrieve all existing relevant literature, we systematically searched not only PubMed, but also EMBASE and Web of Science, which yield "gray literature" (abstracts, theses, etc.) that cannot be found in Pubmed.

Even when all searchable literature has been included, it is possible that some studies were never published, not even as abstracts or theses. We used funnel plots, the most commonly used method to detect publication bias. The funnel plot displays the effect size on the x axis and the sample size (or an equivalent measure such as variance or standard error) on the y axis. Larger studies appear toward the top of the funnel plot and generally cluster around the real effect size. Smaller studies appear toward the

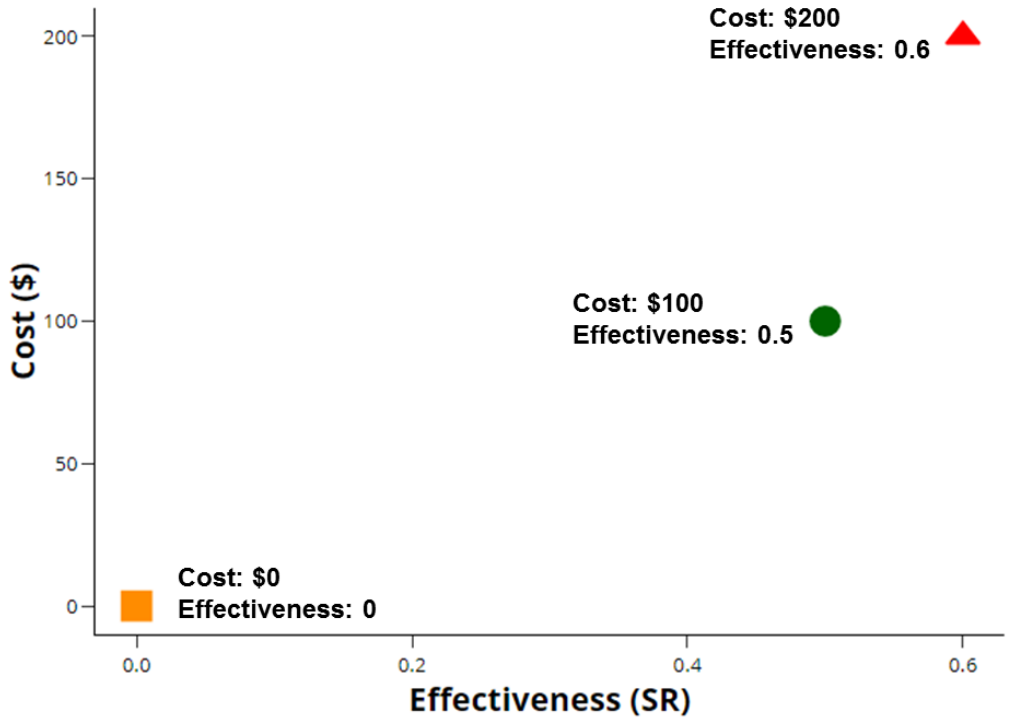
bottom of the graph and tend to be spread across a broad range of values (because smaller studies have more random error variation in the effect size). If there is no publication bias the studies will be distributed symmetrically around the real effect size, since the sampling error is random. In the presence of publication bias the studies are expected to be distributed with symmetry at the top of the funnel plot, a few studies "missing" in the middle, and more studies "missing" near the bottom. "Missing" studies are the studies that probably were conducted but were never published because they had a small effect size, a small sample size, and, therefore, were not statistically significant or because their results were in the opposite direction than the direction the researchers expected. Detection of publication bias through visual evaluation of a funnel plot is somewhat subjective.

In contrast, Duval and Tweedie trim and fill method is an objective algorithm to adjust for publication bias and iteratively calculate the unbiased effect size [8]. Conceptually, the trim and fill method follows two automated steps: first, the algorithm removes (trims) the studies that cause a funnel plot asymmetry, so that the overall estimated effect size produced by the remaining studies is mostly unaffected by publication bias; secondly, using the bias-corrected overall estimate, the algorithm fills the initially trimmed studies and their "missing" counterparts that probably existed but were never published because of publication bias. We used the trim and fill algorithm by Duval and Tweedie with the L_0 estimator [8], and identified the direction of potentially missing studies with the Egger method [9]. For the trim and fill method, we used a fixed-random model, which is a fixed-effect model (less likely to be influenced by small biased studies: publication bias) to trim and fill studies and a random-effects model (more appropriate for studies coming from heterogeneous populations) to estimate the pooled effect of the studies once they are trimmed and filled [10]. In the Duval and Tweedie trim and fill method, the fixed-random model performs better than the fixed-fixed model and no worse and marginally better in certain situations than the random-random model [10].

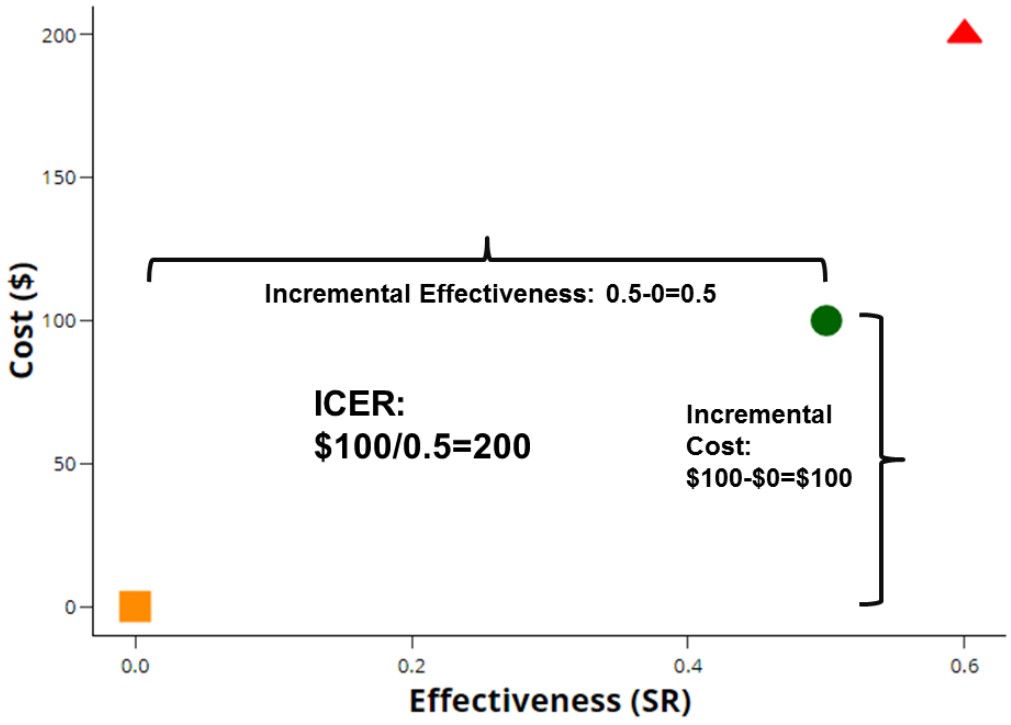
For the cost-effectiveness model, input parameters for effectiveness (estimated from the meta-analysis of multiple studies) were modeled with a beta distribution and input parameters for cost

(estimated from a more limited number of cost sources) were modelled with a triangular distribution. All cost-effectiveness analyses were performed using TreeAge Pro 2015 (TreeAge Software, Inc., Williamstown, MA) [11]. Interactive versions of the meta-analysis and the cost-effectiveness models were created with R packages shiny [12], ggplot2 [4], and plotly [13].

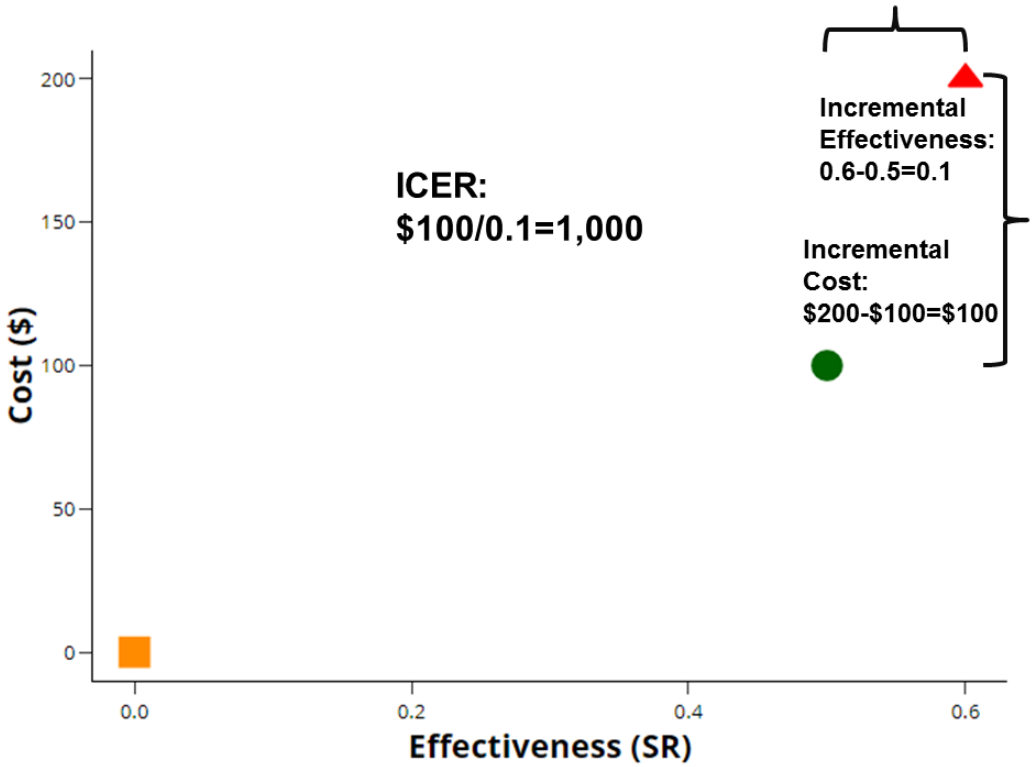
We quantified cost-effectiveness with the incremental cost-effectiveness ratio (ICER). The ICER measures the relative cost-effectiveness of competing treatments by dividing the incremental cost of a treatment (compared to the next most cost-effective treatment) by the incremental effectiveness (compared to the next most cost-effective treatment) [14]. Although detailed explanations of ICER, the efficiency frontier, and dominance are beyond the scope of this study, we provide a graphical explanation to roughly grasp these concepts and we refer the interested reader elsewhere to more in-depth explanations and calculations [14]. First, the ICER is a comparative measure between treatments, not a characteristic of any individual treatment. For illustration purposes, let's calculate the ICER for three treatments with simulated data.



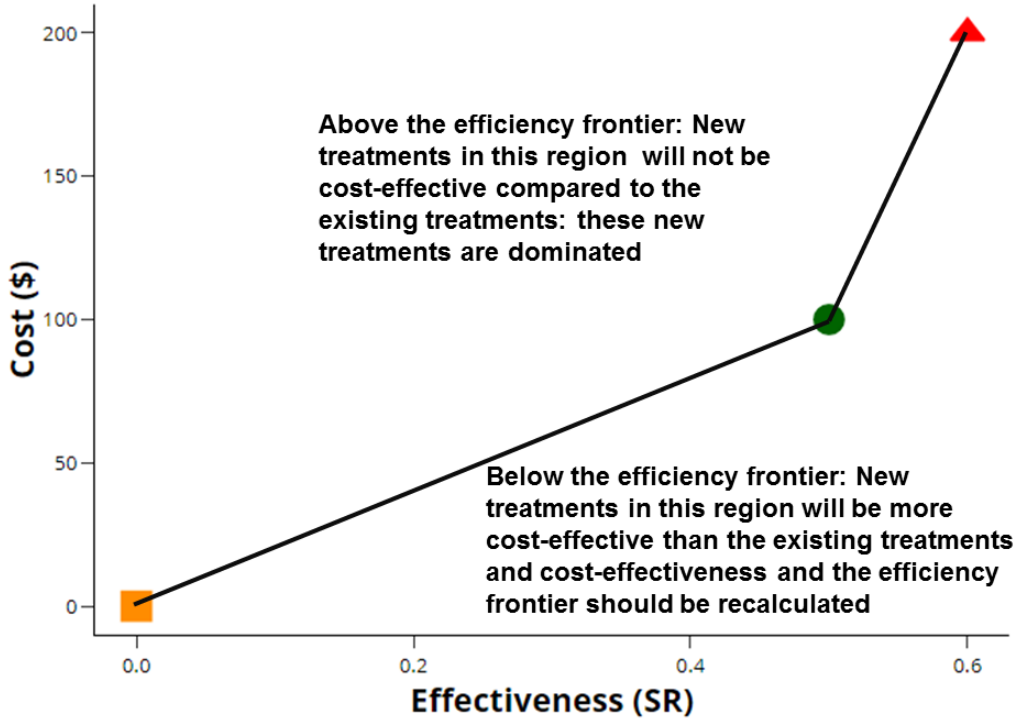
The baseline “no treatment” is the orange square with $0 cost and 0 probability of spasm resolution (SR); the green circle represents “treatment A” with $100 cost and 0.5 probability of spasm resolution; and the red triangle is “treatment B” with $200 cost and 0.6 probability of spasm resolution.



To calculate the ICER of “treatment A” we have to reference cost and effectiveness to the next most cost-effective alternative, which is “no treatment”. The incremental cost is $100-$0 = $100 and the incremental effectiveness is 0.5-0 = 0.5. The ICER is $100/0.5 = 200, that is, $200 will have to be spent per each case of infantile spasms resolved with “treatment A”.



To calculate the ICER of "treatment B" we have to reference cost and effectiveness to the next most cost-effective alternative, which is "treatment A". The incremental cost is $200-$100 = $100 and the incremental effectiveness is 0.6-0.5 = 0.1. The ICER is $100/0.1 = 1,000, that is, $1,000 will have to be spent per each case of infantile spasms resolved with "treatment B". It may seem more intuitive to compare the cost and effectiveness of "treatment B" with the baseline of "no treatment", but that comparison is incorrect in a competing choice problem because it does not take into account that one can obtain an effectiveness of 0.5 at a cost of $100 with "treatment A".



The efficiency frontier is determined by the line that joints the most cost-effective treatments: new treatments above and to the left of the efficiency frontier are not cost-effective compared to the existing treatments. In contrast, new treatments below and to the right of the efficiency frontier are more cost-effective than the existing treatments and, in case that these new treatments appear, a new calculation of cost-effectiveness and of the efficiency frontier should be performed.

For more details on how ICER is calculated, the difference between a competing choice and a shopping spree problem, implications of the efficiency frontier, and the difference between absolute

dominance and extended dominance, we refer the reader to a more in-depth textbook on decision analysis [14].

We also provided intuitive measures of effect such as the number needed to treat and its clinical meaning and the ratio of ICER of the compared options and their clinical meaning.

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