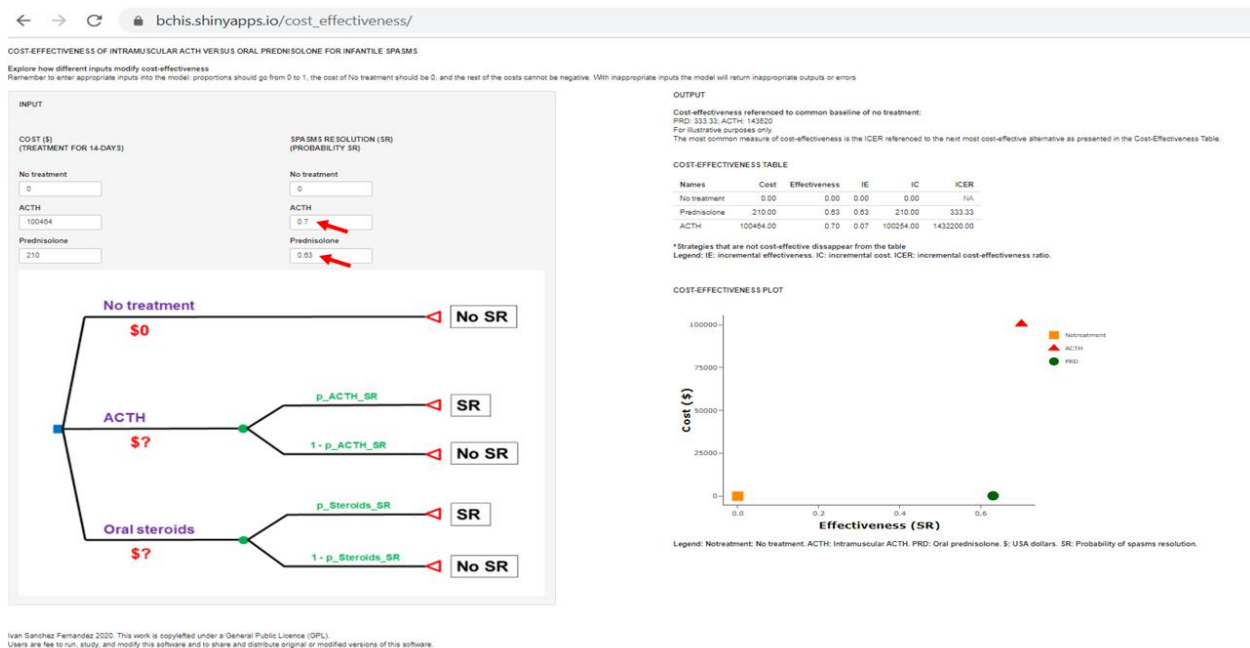


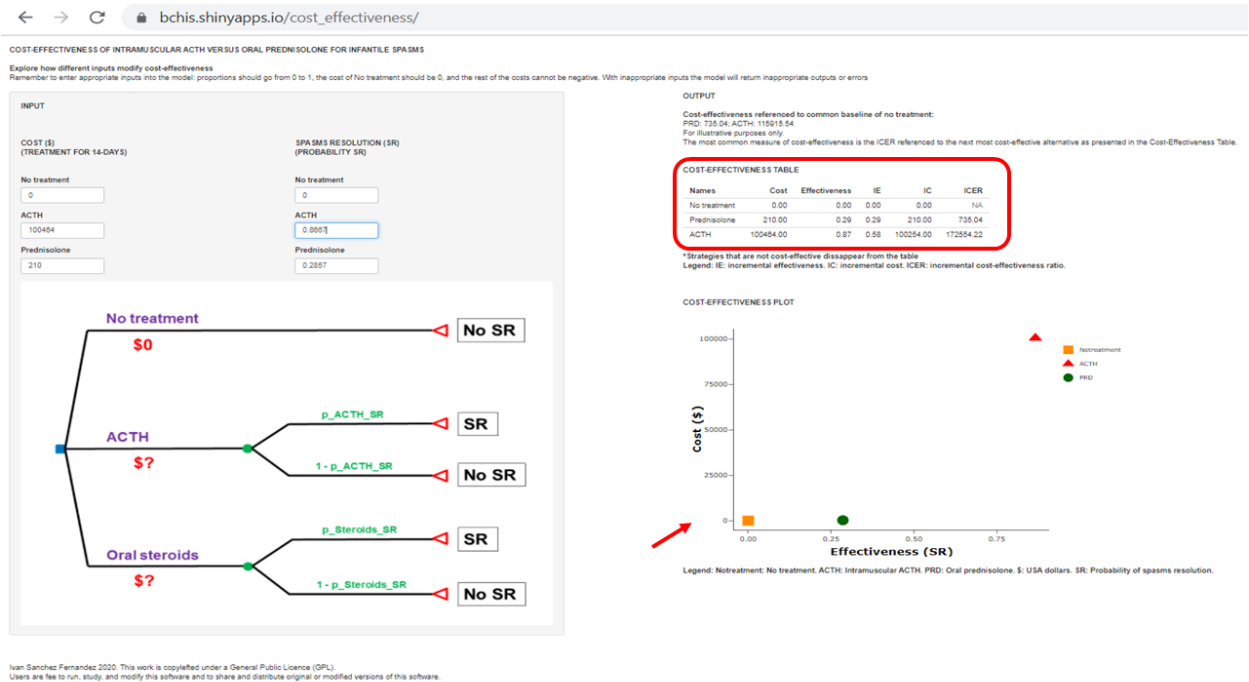
MODIFYING EFFECTIVENESS S1. EFFECTIVENESS OF ACTH AND PREDNISOLONE

Different estimations of effectiveness. If different estimations of cost and effectiveness become available or are more appropriate for the reader's specific setting, the reader can enter these values at https://bchis.shinyapps.io/cost_effectiveness/

Let's modify the default values for the effectiveness of ACTH and Prednisolone.



Let's enter, for example, an effectiveness for ACTH of 0.8667 and an effectiveness for oral prednisone of 0.2857, (based on Baram et al, 1996¹, the study where ACTH effectiveness was highest compared to oral steroids).



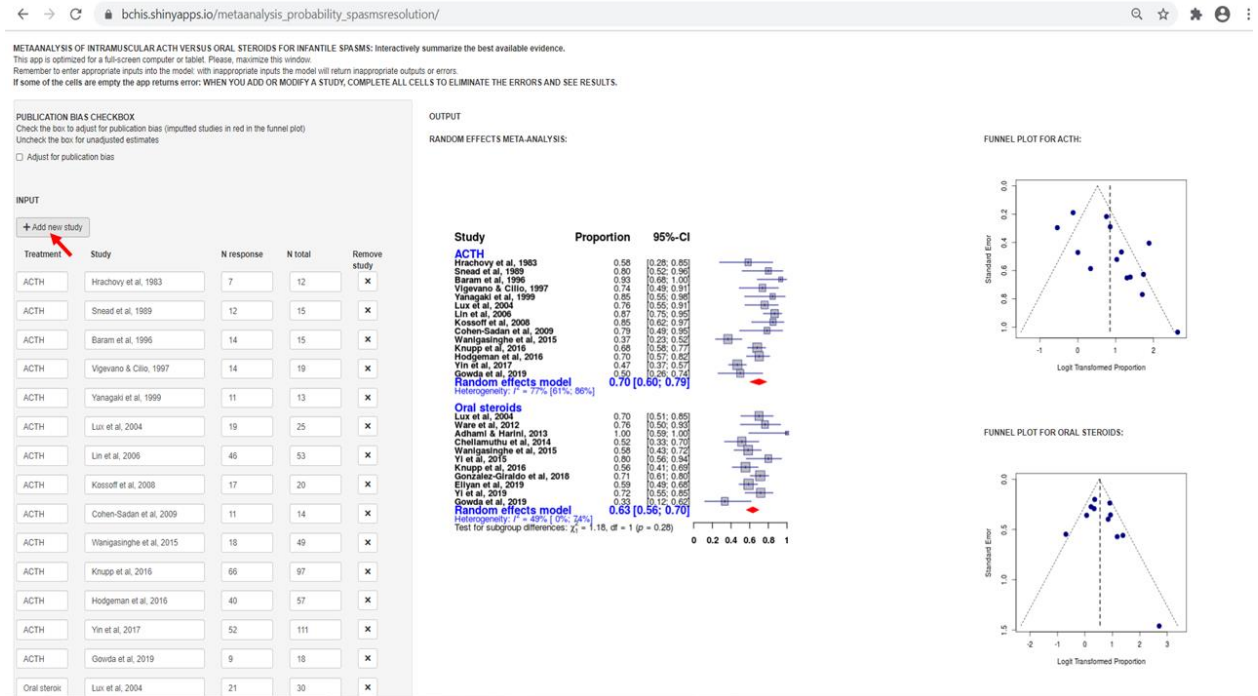
The app will recalculate the cost-effectiveness values and redraw the graph. As a side note, using the study with the most extreme results is not going to provide a fair representation of reality, but serves as an exercise of what would the cost-effectiveness be in the most extreme scenario.

The same process can be done for the strategies cost-effectiveness at https://bchis.shinyapps.io/cost_effectiveness_strategies/

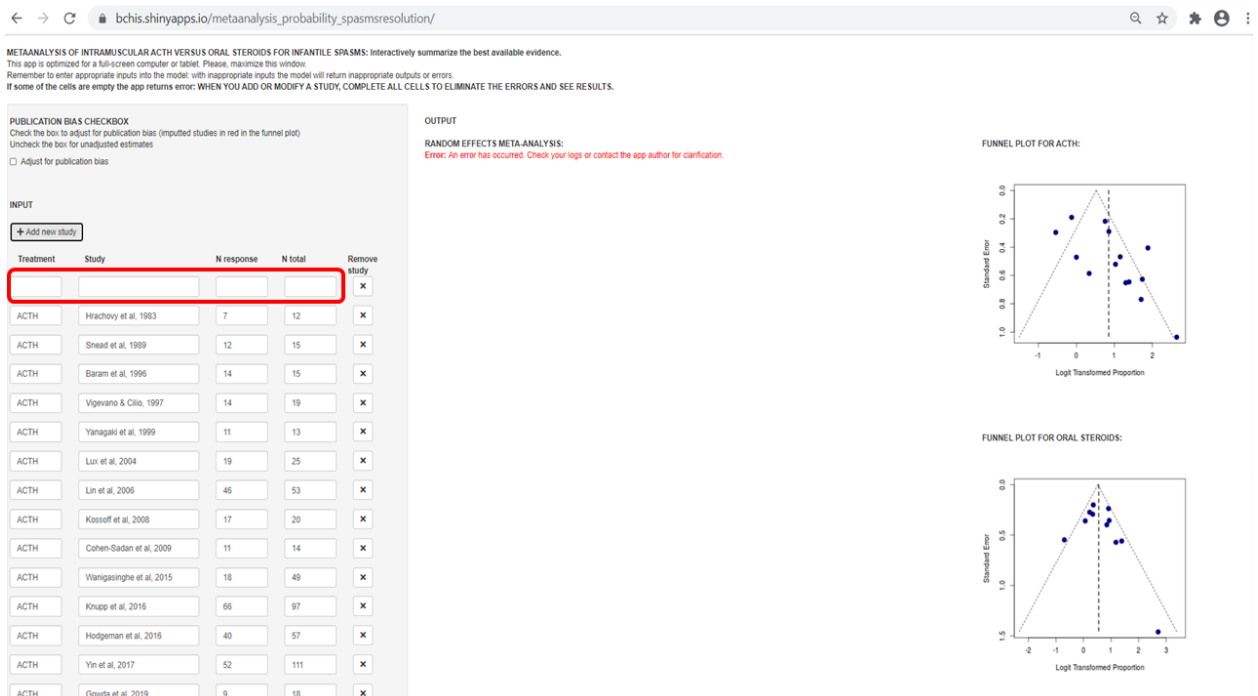
Future studies. When future studies become available, they can be incorporated into the analysis. Let's assume that InvestigatorA et al publish a new study on the effectiveness of Prednisolone in 2024 and this study shows that of the 50 patients treated with oral prednisolone, 40 became free from clinical spasms at 14 days. We can easily incorporate these data into the meta-analysis going to https://bchis.shinyapps.io/metaanalysis_probability_spasmsresolution/

There the reader will find the initial screen of the interactive app.

Cost-Effectiveness Infantile Spasms

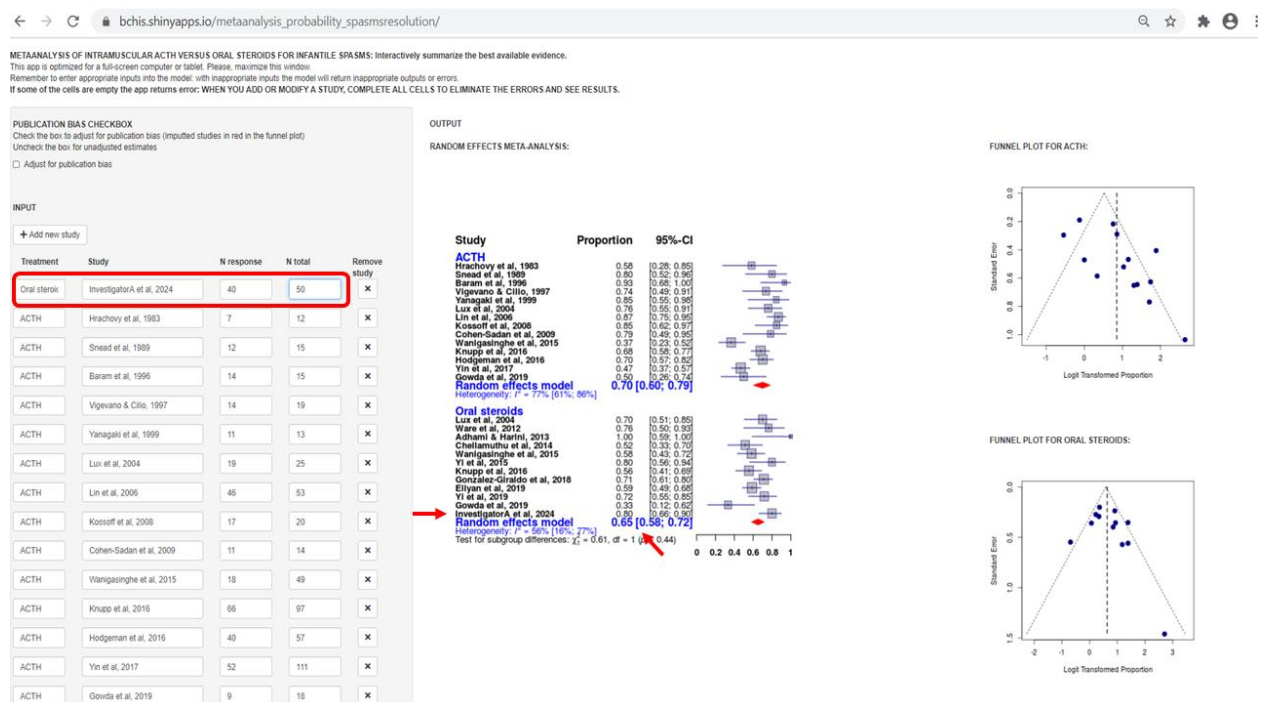


Click on “+ Add new study” (red arrow in the image above) to create a new slot for the new study (red square below):



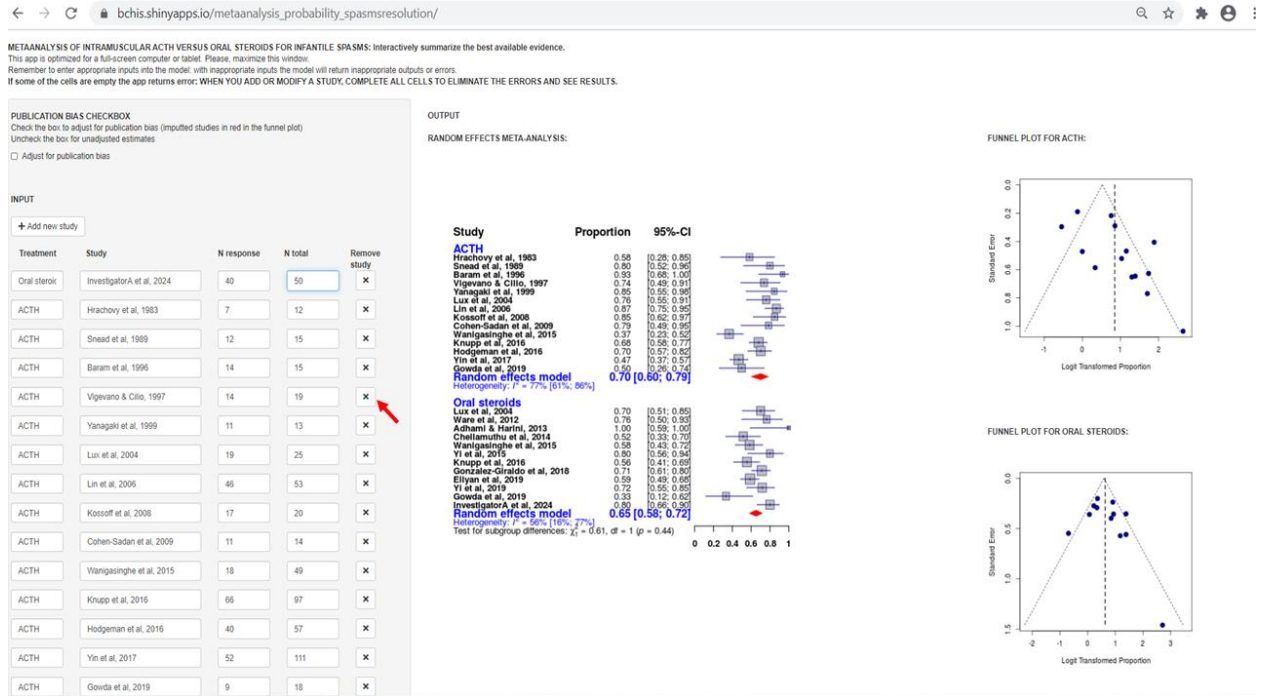
Do not worry about the error message “Error: An error has occurred. Check your logs or contact the app author for clarification”. It simply means that currently there are no data for that new study and, therefore, the app cannot calculate the new results. Let’s give the app the data of the new study.

Enter the treatment (in this case “Oral steroids”), study name (in this case, “InvestigatorA et al, 2024”), the number of patients who responded (in this case, 40 [should be a number]), and the total number of patients (in this case, 50 [should be a number]). The app will automatically incorporate the new study and recalculate all values in the meta-analysis.

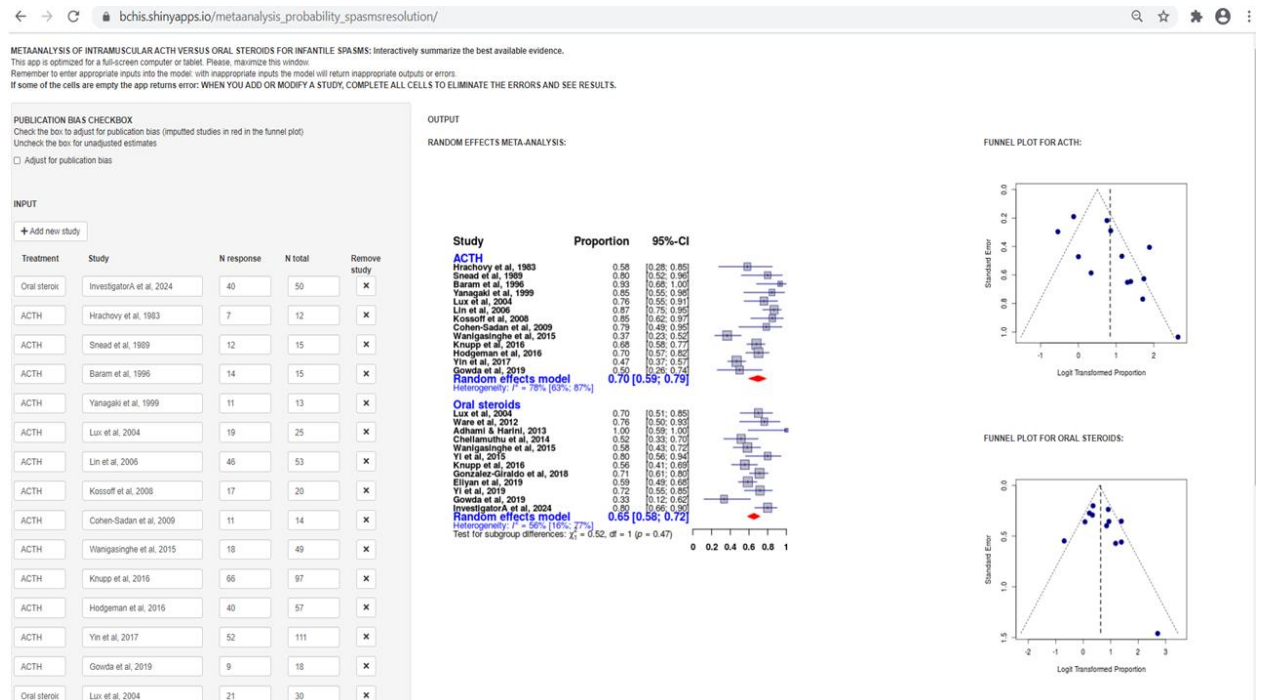


There you have it! The new study is in the meta-analysis that now has recalculated all values (arrows) and funnel plots. The reader can add as many new studies as you want. The reader can also delete studies if you think they are not representative. Just click on the “Remove study” “X” for that study (red arrow below):

Cost-Effectiveness Infantile Spasms



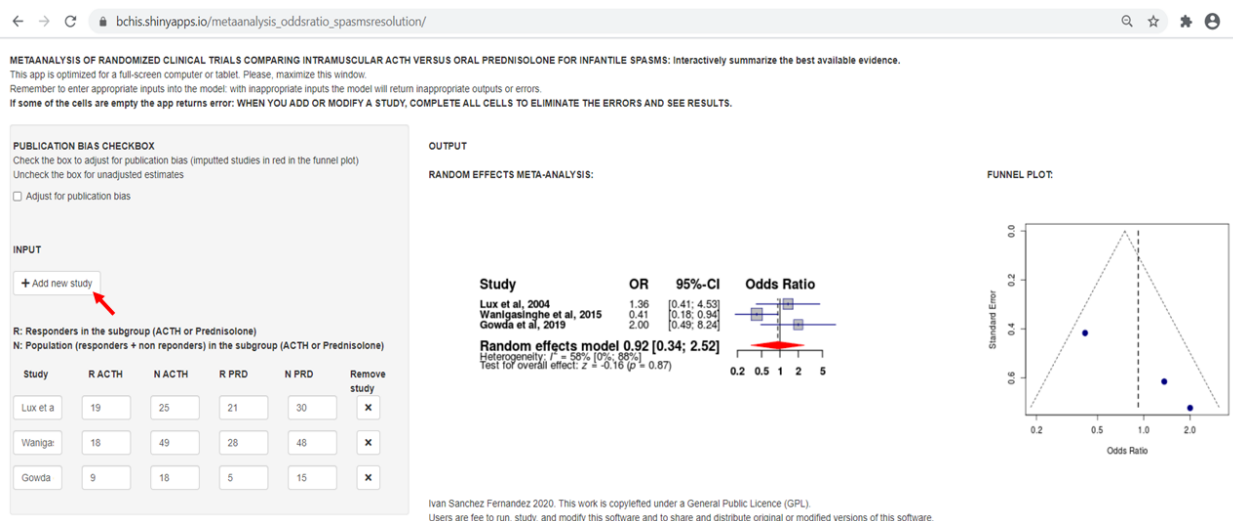
The study will no longer be considered and all values will be recalculated.



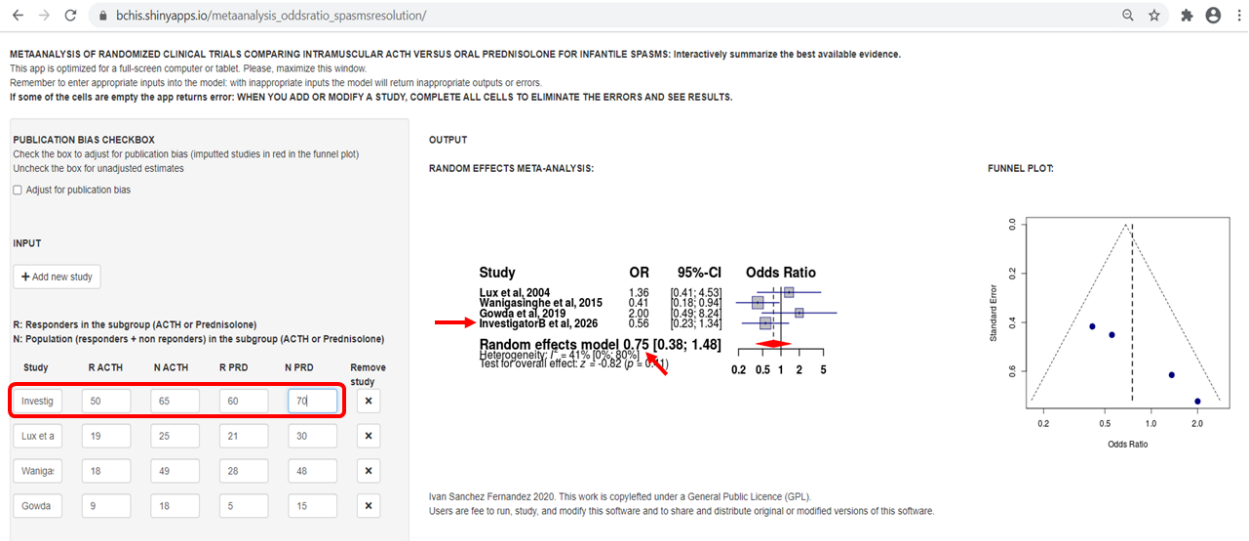
The reader can add and delete as many studies as needed.

Now, let's assume that InvestigatorB et al publish a new randomized clinical trial in 2026 in which Prednisolone resolves clinical spasms at 14 days in 60 of 70 patients and ACTH resolves clinical spasms at 14 days in 50 of 65 patients. The reader can go to

https://bchis.shinyapps.io/metaanalysis_oddsratio_spasmsresolution/

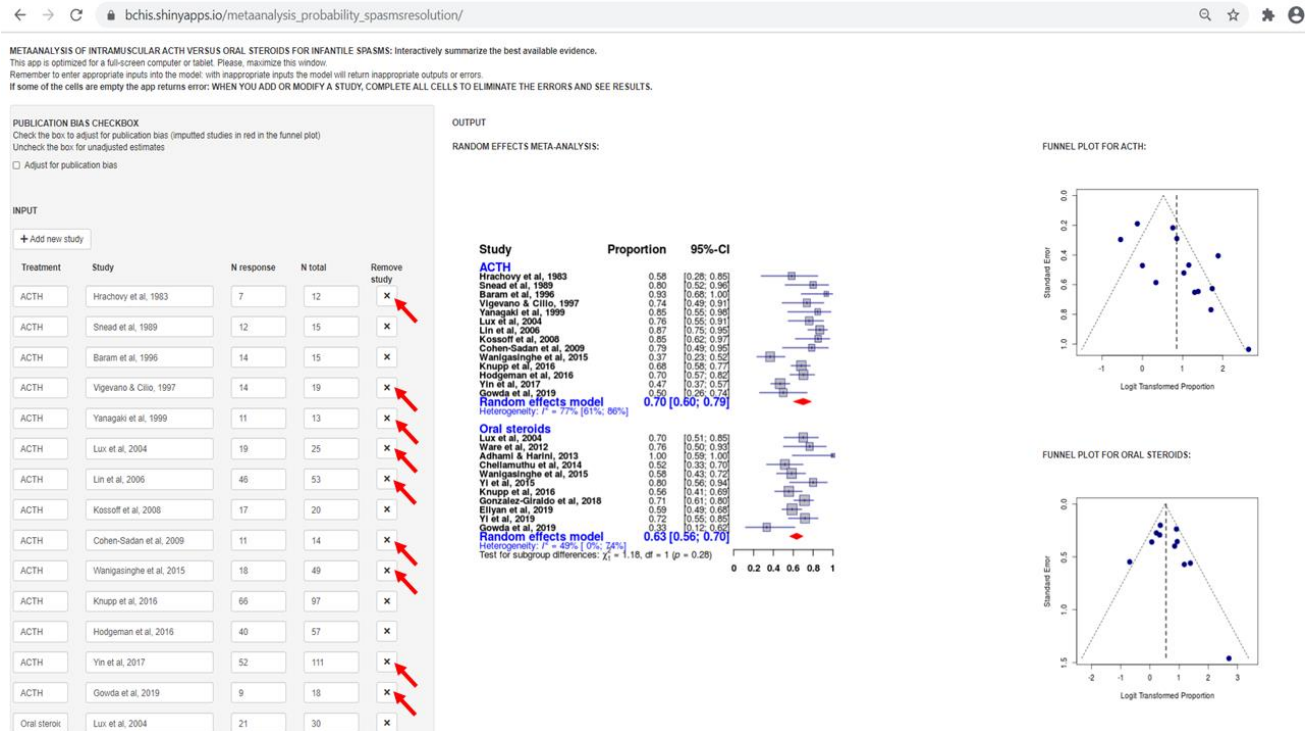


Click on the “+ Add new study” (red arrow in the image above) to create a new slot for the new study. Enter the study name (in this case, “InvestigatorB et al, 2026”), the number of patients who responded to ACTH (in this case, 50 [should be a number]), the total number of patients on the ACTH arm (in this case, 65 [should be a number]), the number of patients who responded to Prednisolone (in this case, 60 [should be a number]), and the total number of patients on the Prednisolone arm (in this case, 70 [should be a number]).

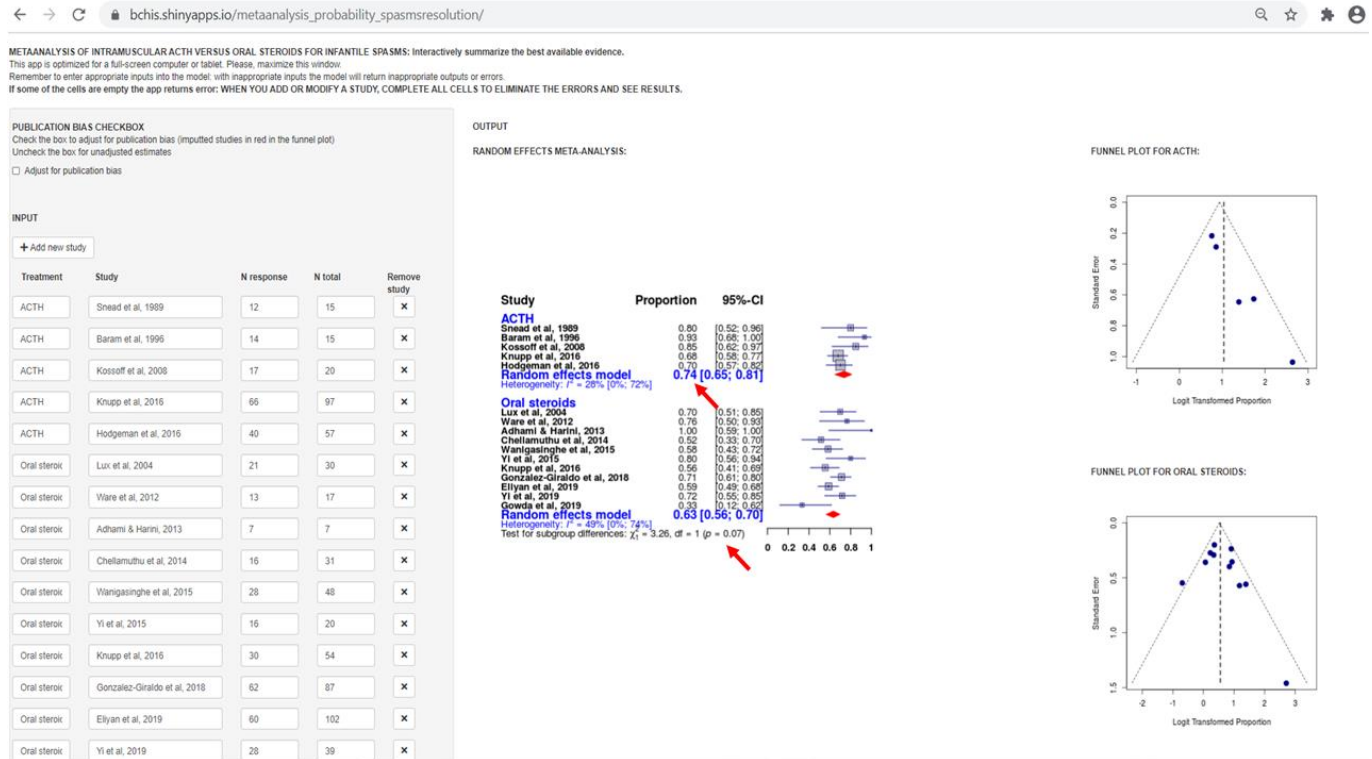


The app will automatically incorporate the new study and recalculate all values in the meta-analysis. The reader can also add and delete as many studies as needed in this meta-analysis of randomized clinical trials.

Analyses considering only studies with certain characteristics. If the reader considers only studies in which ACTH was natural (not synthetic) and only at a dose of 150 IU/m²/day, the reader can go to https://bchis.shinyapps.io/metaanalysis_probability_spasmsresolution/ and eliminate all studies on ACTH that do not meet these requirements by clicking on the “Remove study” “X” (red arrows in the image below):



The resulting analysis will only consider 4 studies for ACTH: Snead et al, 1989², Baram et al, 1996¹, Kossoff et al, 2008³, and Knupp et al, 2016⁴ because these are the only studies with natural ACTH at 150 IU/m²/day. The results of this analysis still show that the estimated efficacy of ACTH: 0.74 (95% CI: 0.65 to 0.81) is not statistically significantly different than the estimated effectiveness of oral steroids: 0.63 (95% CI: 0.56 to 0.70), $p=0.07$ (red arrows in the figure below).



When performing these analyses the reader should always try to include all relevant literature, as we did in the main analysis.

REFERENCES

1. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics* 1996;97:375-9.
2. Snead OC, 3rd, Benton JW, Jr., Hosey LC, Swann JW, Spink D, Martin D, et al. Treatment of infantile spasms with high-dose ACTH: efficacy and plasma levels of ACTH and cortisol. *Neurology* 1989;39:1027-31.
3. Kossoff EH, Hedderick EF, Turner Z, Freeman JM. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia* 2008;49:1504-9.
4. Knupp KG, Coryell J, Nickels KC, Ryan N, Leister E, Loddenkemper T, et al. Response to treatment in a prospective national infantile spasms cohort. *Ann Neurol* 2016;79:475-84.