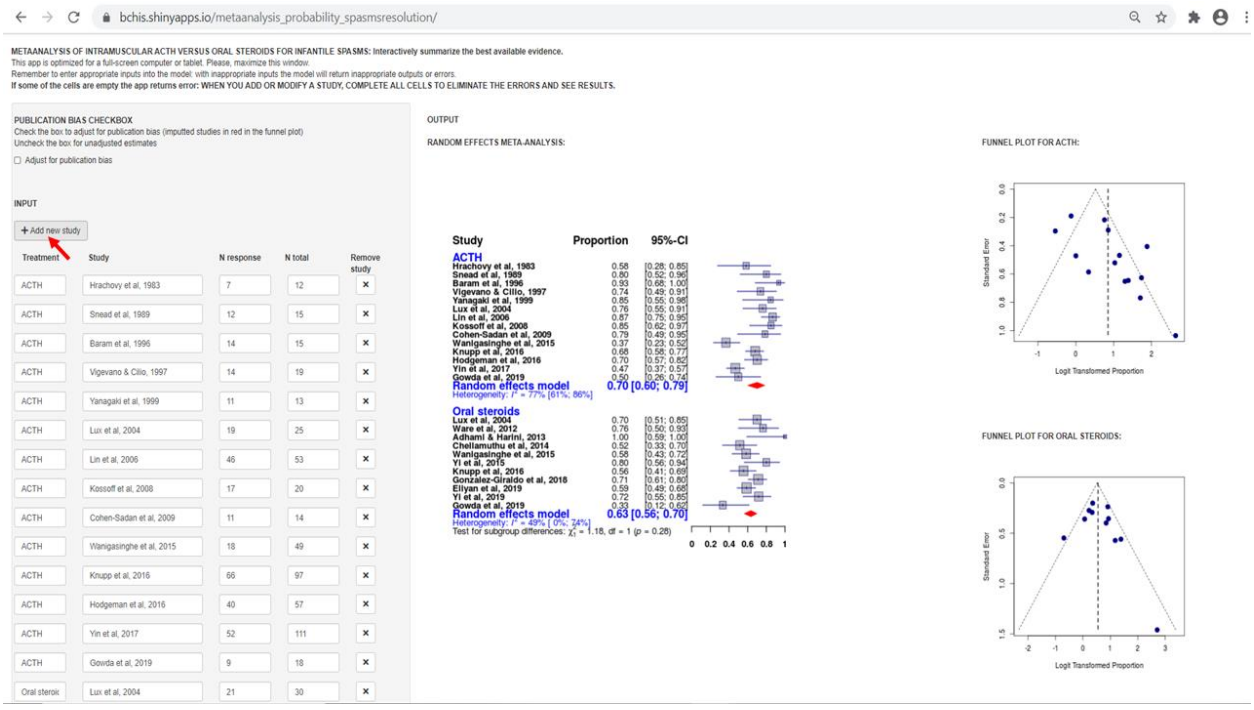
INTERACTIVE ANALYSIS EXAMPLE

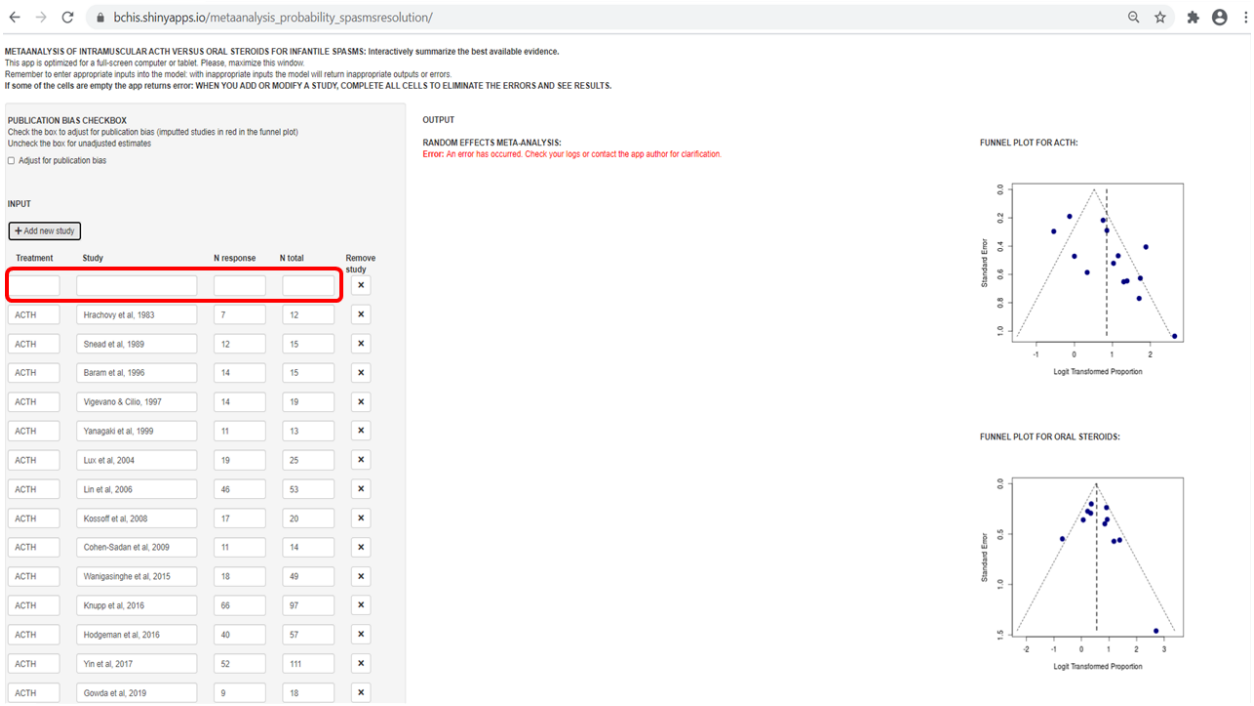
Background. We have created interactive tools for the readers to evaluate in real time how new data, different estimations of effectiveness, or different estimations of prices modify the conclusions of the analysis. Here we provide a step-by-step approach to their use.

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 you will find the initial screen of the interactive app.

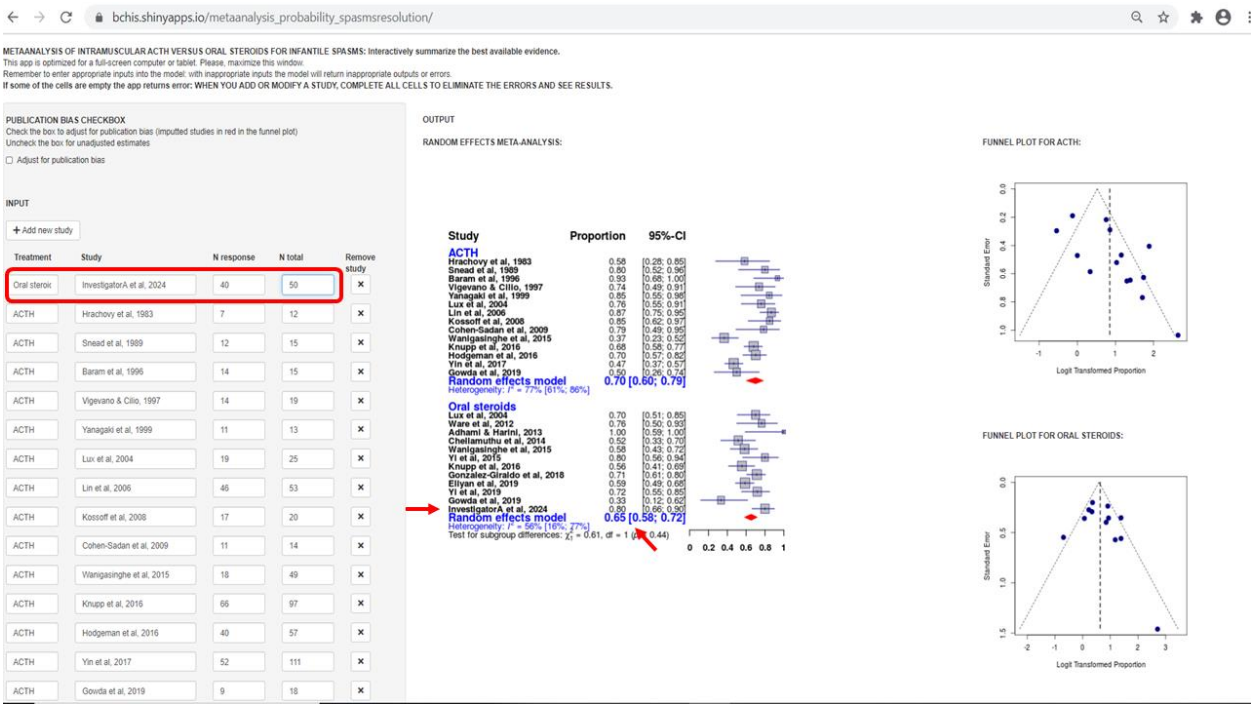


Click on "+ Add new study" (red arrow in the image above) to create a new slot for the new study (red square below):

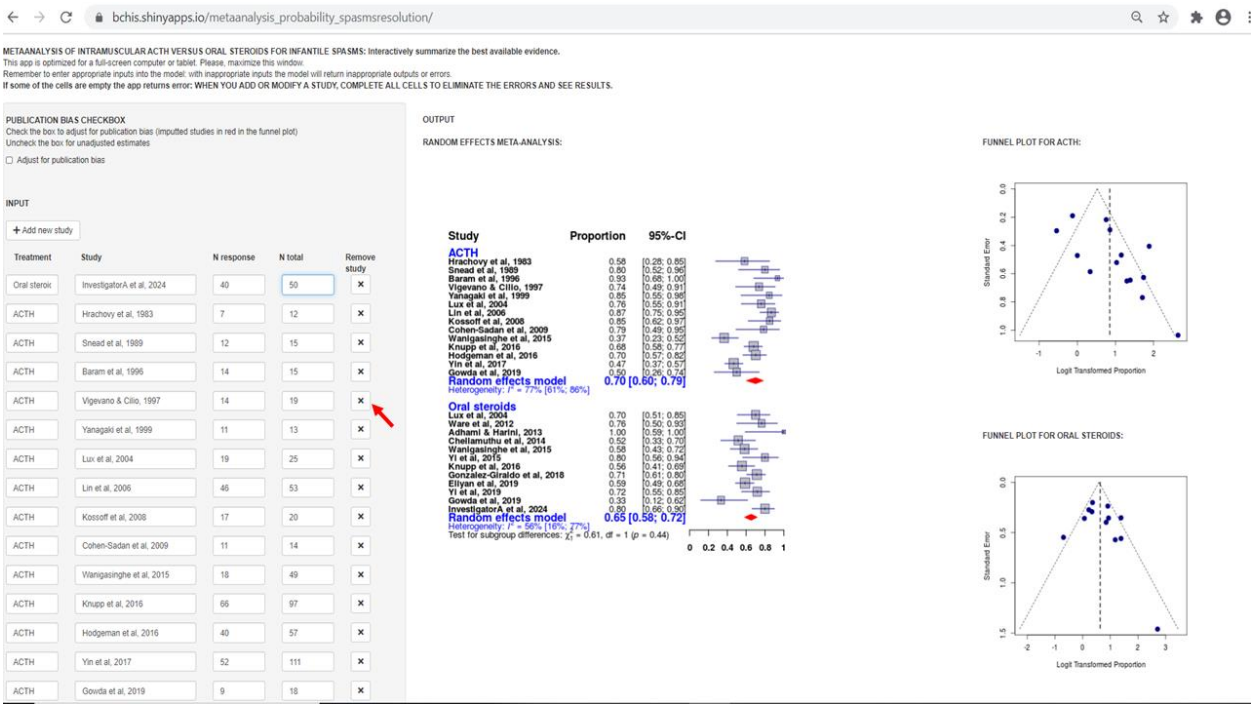


Do not worry about the error message "Error: An error has occurred. Check your logs or contact the app author for clarification". It simply means that currently there are no data for that new study and, therefore, the app cannot calculate the new results. Let's give the app the data of the new study.

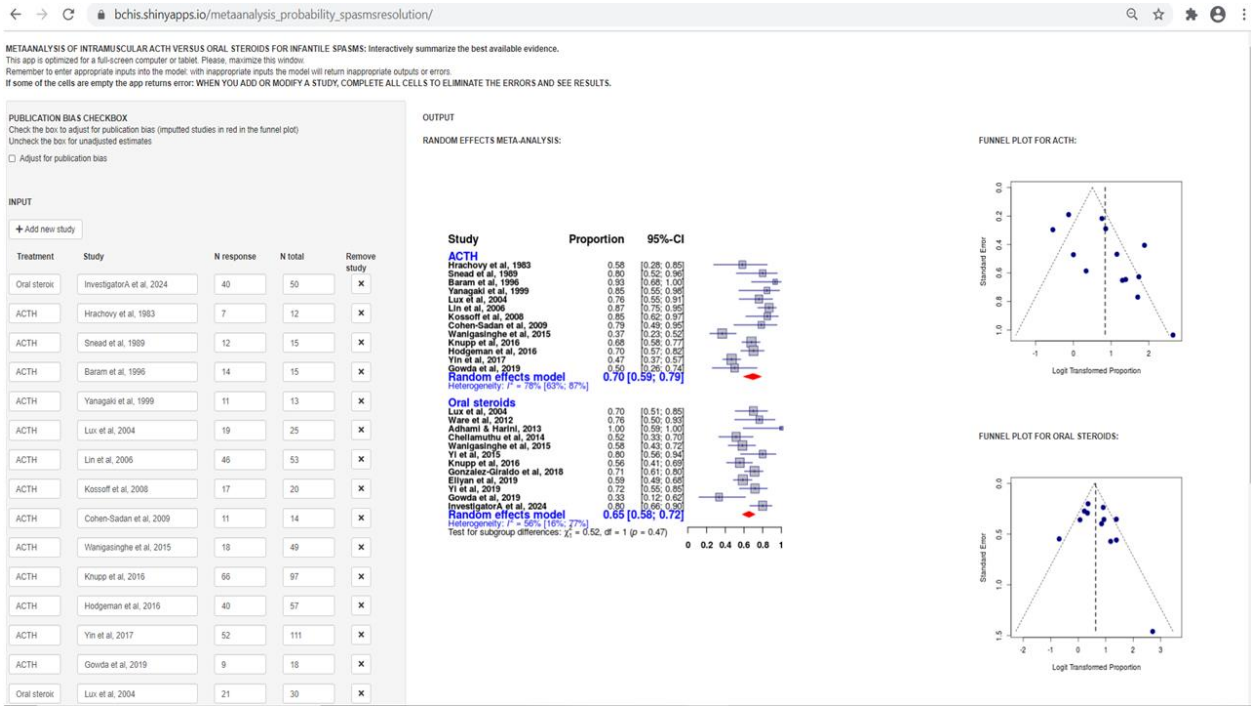
Enter the treatment (in this case "Oral steroids"), study name (in this case, "InvestigatorA et al, 2024"), the number of patients who responded (in this case, 40 [should be a number]), and the total number of patients (in this case, 50 [should be a number]). The app will automatically incorporate the 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. You can add as many new studies as you want. You can also delete studies if you think they are not representative. Just click on the "Remove study" "X" for that study (red arrow below):

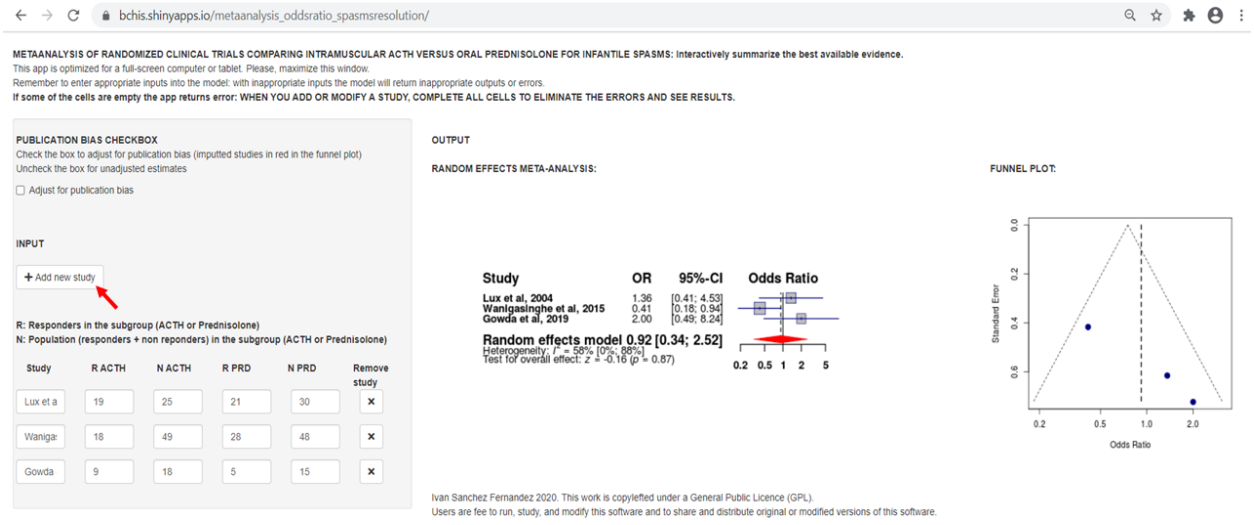


The study will no longer be considered and all values will be recalculated.

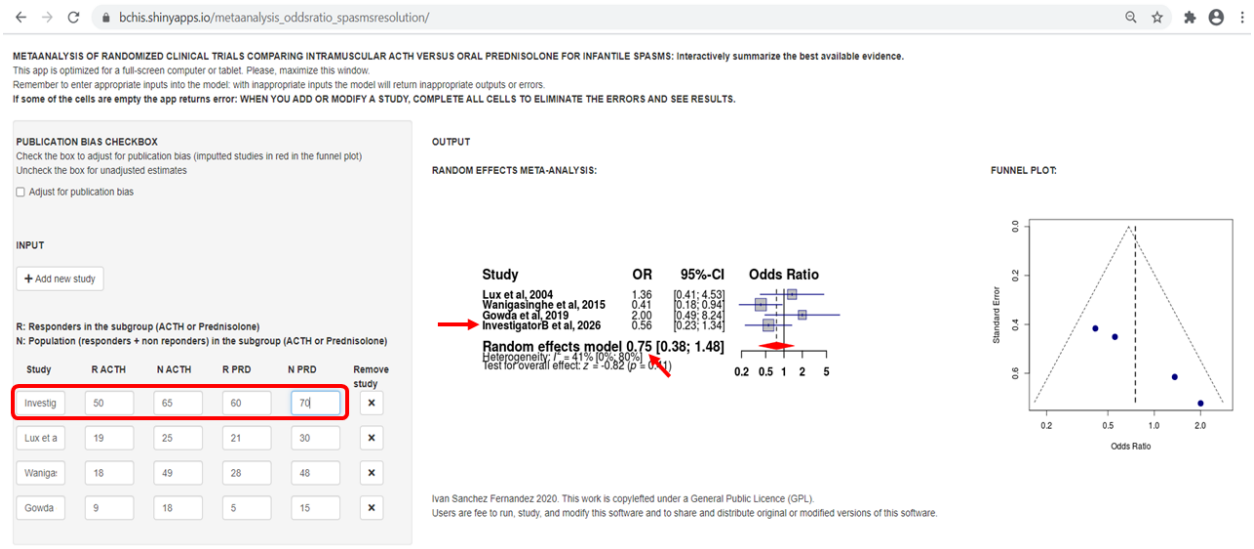


You can add and delete as many studies as you like.

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. You can go to https://bchis.shinyapps.io/metaanalysis_oddsratio_spasmsresolution/



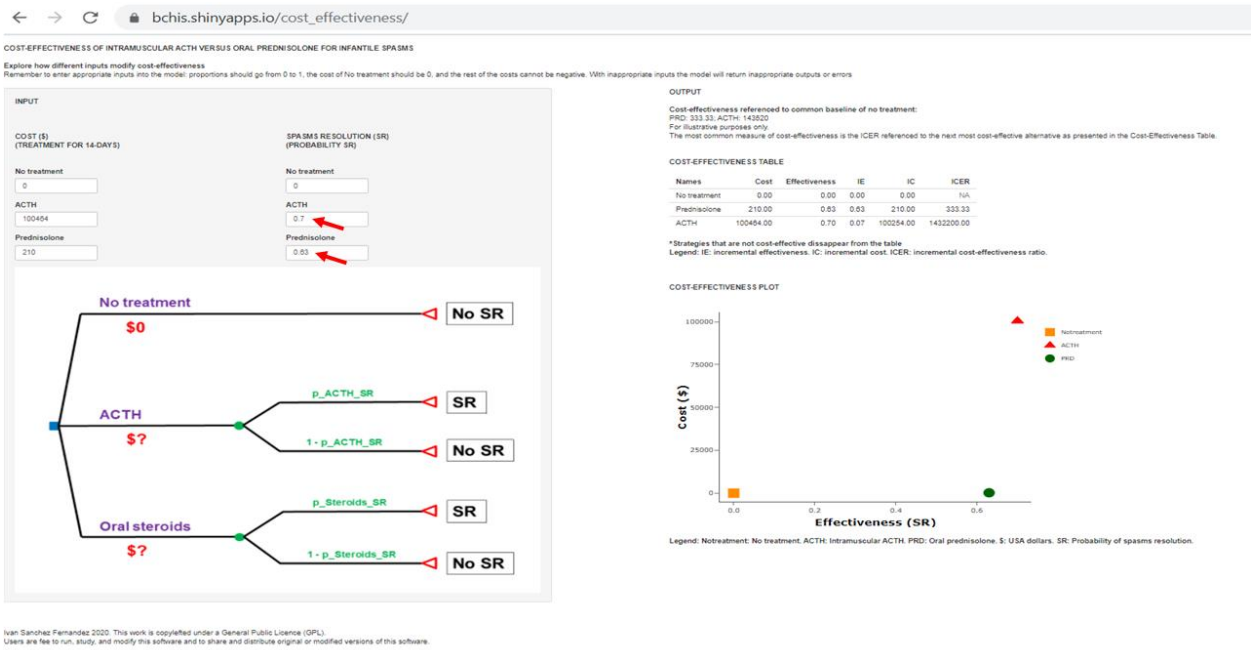
Click on the "+ Add new study" (red arrow in the image above) to create a new slot for the new study. Enter the study name (in this case, "InvestigatorB et al, 2026"), the number of patients who responded to ACTH (in this case, 50 [should be a number]), the total number of patients on the ACTH arm (in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



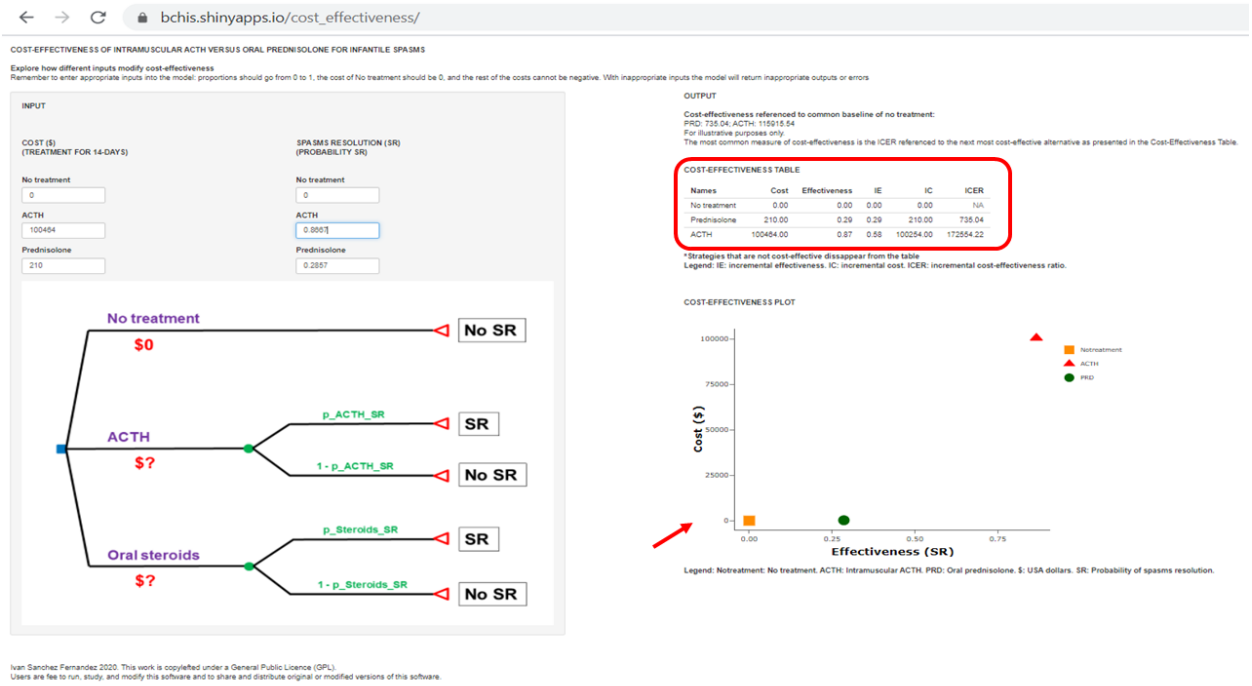
The app will automatically incorporate the new study and recalculate all values in the meta-analysis. You can also add and delete as many studies as you like in this meta-analysis of randomized clinical trials.

Different estimations of cost and effectiveness. Similarly, if different estimations of cost and effectiveness become available or are more appropriate for your specific setting, you can enter these values at https://bchis.shinyapps.io/cost_effectiveness/

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

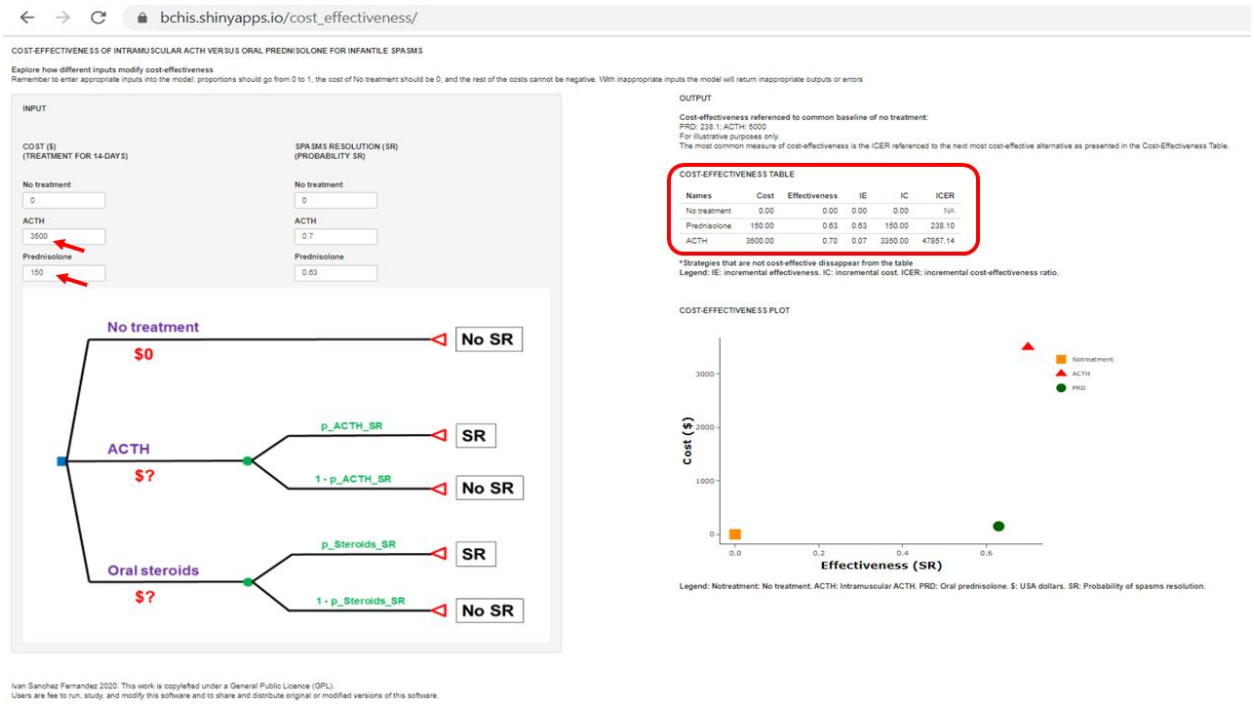


Let's enter, for example, an effectiveness for ACTH of 0.8667 and an effectiveness for oral prednisone of 0.2857, (based on Baram et al, 1996 [1], the study where ACTH was highest compared to oral steroids).



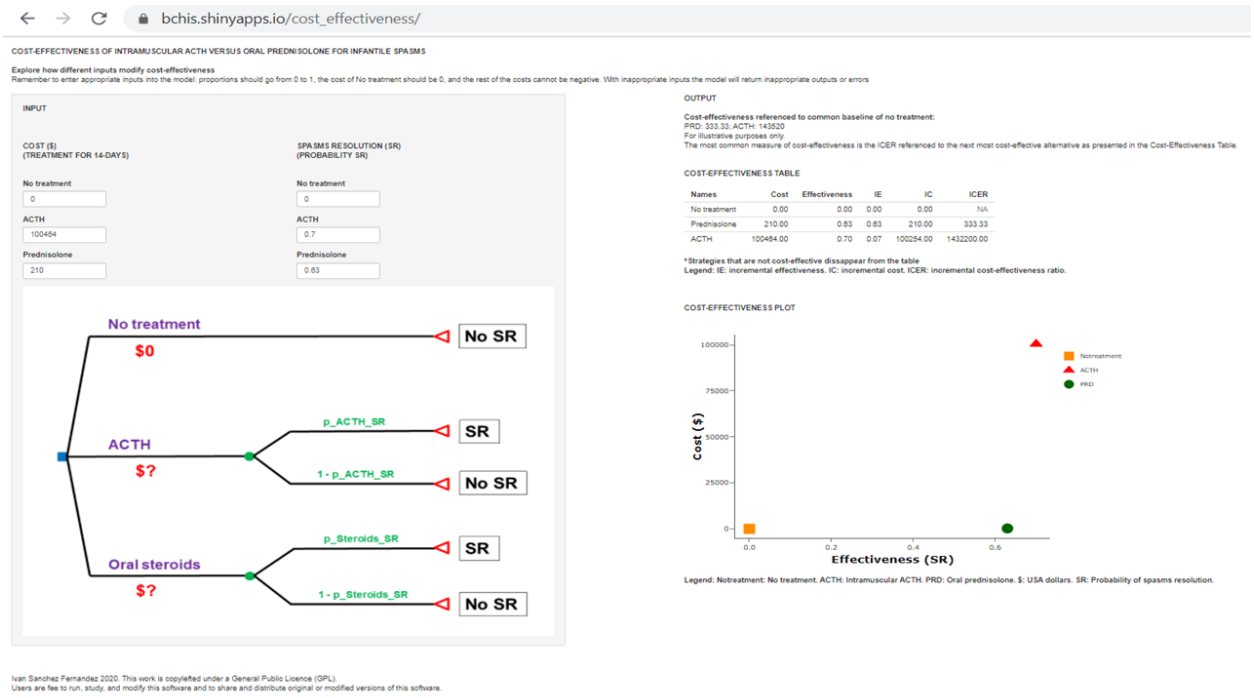
The app will recalculate the cost-effectiveness values and redraw the graph. As a side note, using the study with the most extreme results is not going to provide a fair representation of reality, but serves as an exercise of what would the cost-effectiveness be in the most extreme scenario.

The same can be done modifying the inputs for cost. For example, let's imagine that a reader wants to evaluate the cost-effectiveness of ACTH versus oral prednisolone in another country. Let's imagine that in the reader's country ACTH costs 3,500 in local currency for a 14-course treatment, while the cost of oral prednisolone is 150 in local currency for a 14-day course treatment. If one goes to https://bchis.shinyapps.io/cost_effectiveness/ and enters these values, the result is that oral prednisolone would be the most cost-effective alternative followed by ACTH. The reader can modify values to adapt the analysis to local prices, including prices in different currencies.

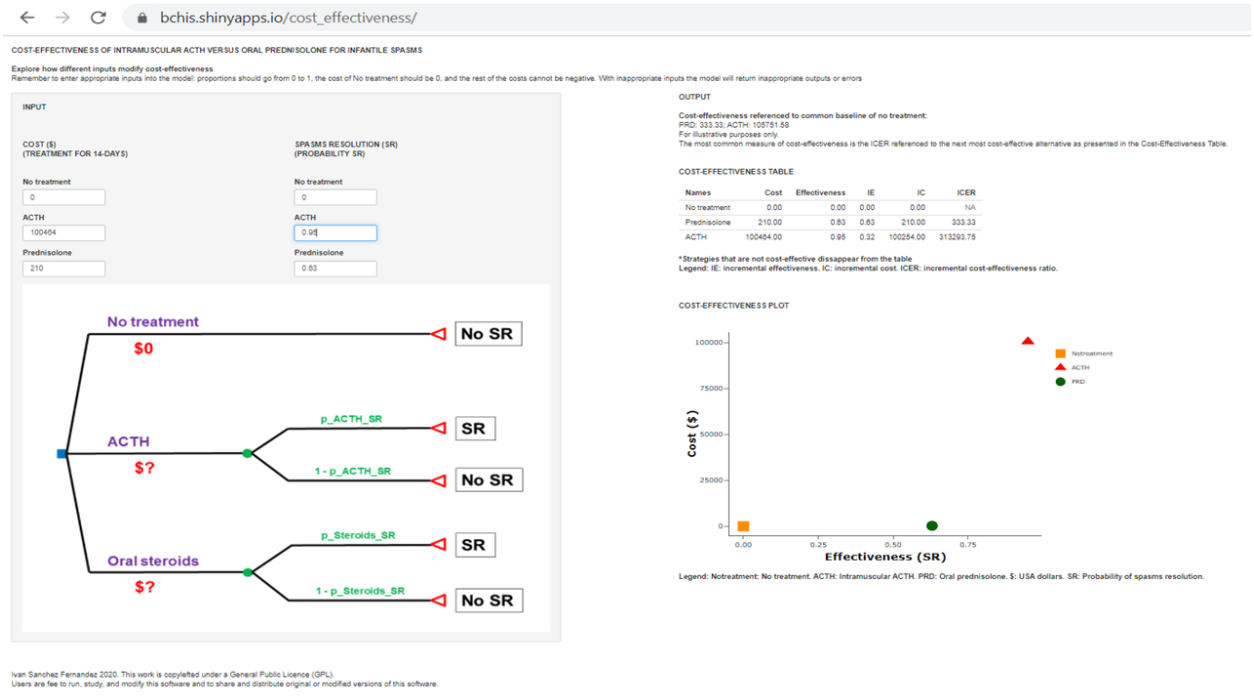


The same process can be done for the strategies cost-effectiveness at https://bchis.shinyapps.io/cost_effectiveness_strategies/

Hypothetical situations. The interactive apps allow the reader to explore hypothetical situations. For example, if the effectiveness of ACTH was higher, when would it become more cost-effective than oral prednisolone? Let's go to https://bchis.shinyapps.io/cost_effectiveness/



And let's assume that the effectiveness of ACTH is much higher (for example 0.95). Let's enter that value in the app and see what the results are:



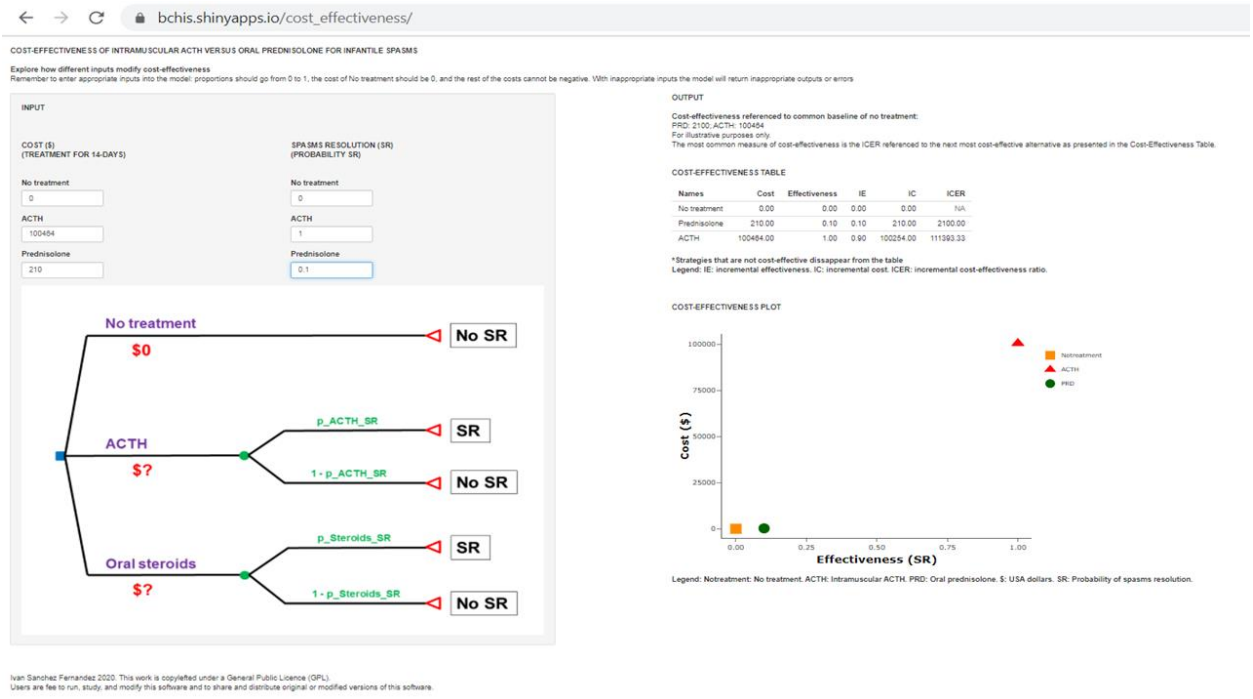
The most cost-effective option remains oral prednisolone with an ICER of $333/SR, while the cost-effectiveness of ACTH is much less favorable at $313,294/SR.

COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No treatment	0.00	0.00	0.00	0.00	NA
Prednisolone	210.00	0.63	0.63	210.00	333.33
ACTH	100464.00	0.95	0.32	100254.00	313293.75

*Strategies that are not cost-effective dissappear from the table
Legend: IE: incremental effectiveness. IC: incremental cost. ICER: incremental cost-effectiveness ratio.

And now let's assume that the effectiveness of oral prednisolone is very low (0.1) and the effectiveness of ACTH is 1 (it resolves clinical spasms in all patients):



The most cost-effective remains oral prednisolone with an ICER of $2,100/SR, while the cost-effectiveness of ACTH is much less favorable with an ICER of $111,393/SR.

COST-EFFECTIVENESS TABLE

Names	Cost	Effectiveness	IE	IC	ICER
No treatment	0.00	0.00	0.00	0.00	NA
Prednisolone	210.00	0.10	0.10	210.00	2100.00
ACTH	100464.00	1.00	0.90	100254.00	111393.33

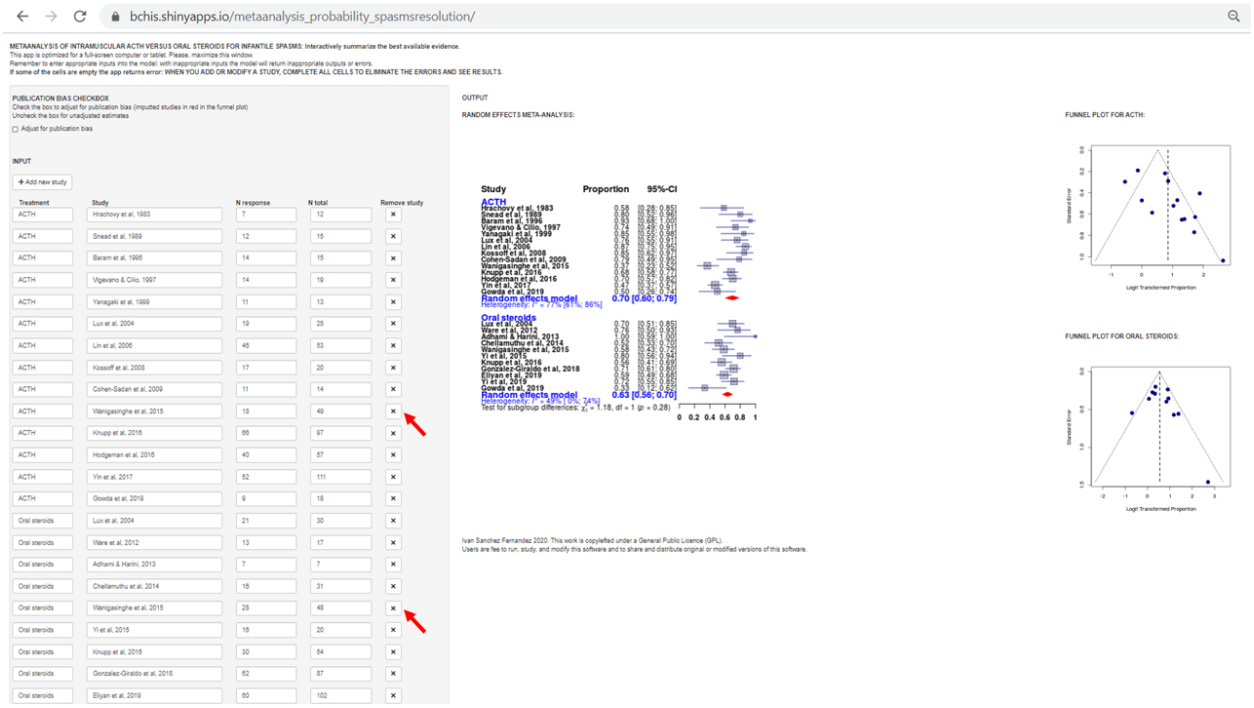
*Strategies that are not cost-effective dissappear from the table
Legend: IE: incremental effectiveness. IC: incremental cost. ICER: incremental cost-effectiveness ratio.

So, not even assuming unrealistic values for the effectiveness of ACTH and oral prednisolone, ACTH does not become the most cost-effective option. This can be better understood if one realizes that ACTH is approximately 500 times more expensive than oral prednisolone. There is no situation where the effectiveness of ACTH will be 500 times more effective than oral prednisolone.

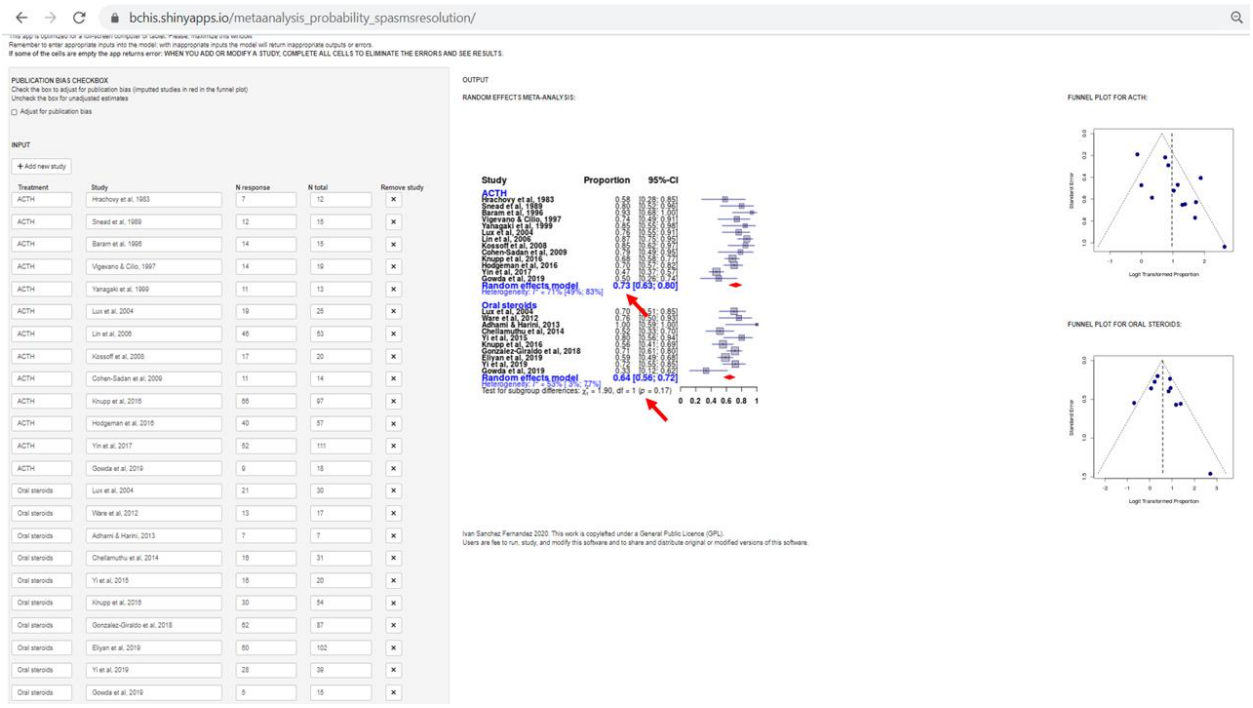
Analyses excluding some studies. If the reader considers that a study (or several studies) are not representative, they can evaluate how the results change without considering these studies. Wanigasinghe et al, 2015 [2] is the largest randomized clinical trial on this topic, but for the sake of argument, let's assume that it is not a representative study because the population is different than in other studies or the medication is different than in other studies. The reader can go to

https://bchis.shinyapps.io/metaanalysis_probability_spasmsresolution/

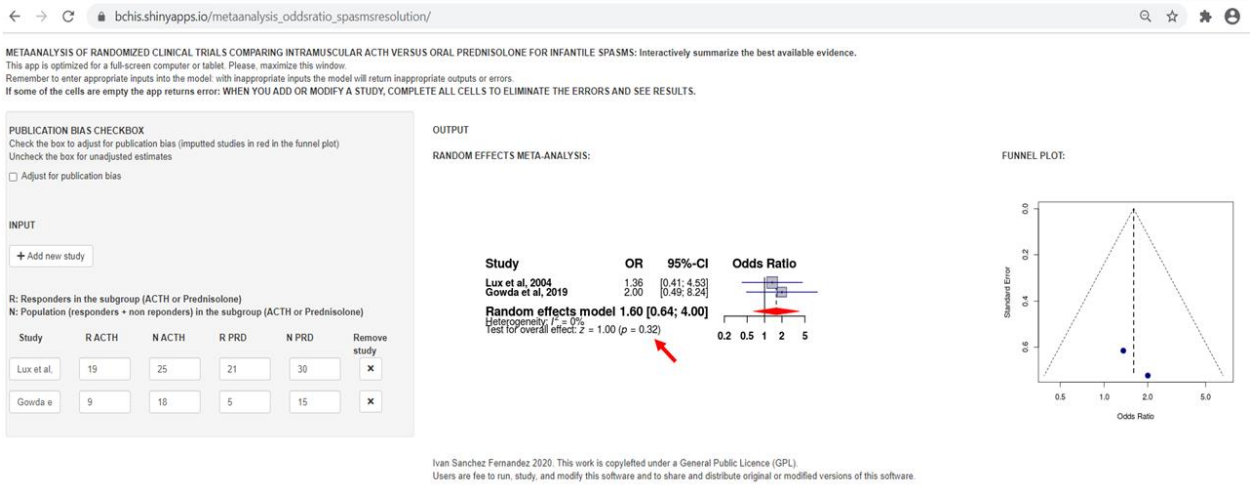
and eliminate the study clicking on the "Remove study" "X" for the data for ACTH and oral steroids (red arrows in the image below):



The results continue to show that the estimated effectiveness of ACTH: 0.73 (95% CI: 0.63 to 0.80) is not statistically significantly different than the estimated effectiveness of oral steroids: 0.64 (95% CI: 0.56 to 0.72), *p*=0.17 (red arrows in the figure below).

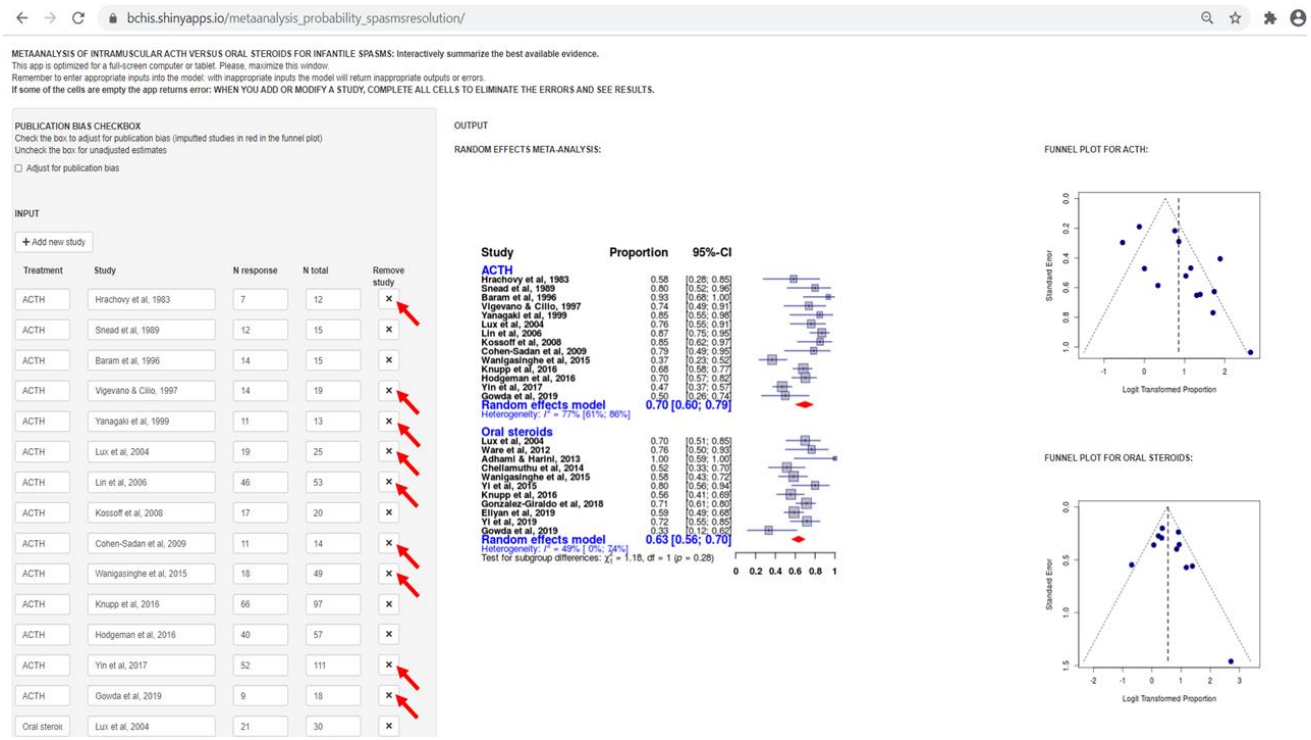


The same process can be done considering the randomized clinical trials. If we exclude Wanigasinghe et al, 2015 [2] clicking on "Remove study" "X", the results still show no statistically significant difference between ACTH and oral prednisolone with an OR 1.60 (95% CI: 0.64 to 4.00) and *p*=0.32 (red arrow in the image below).

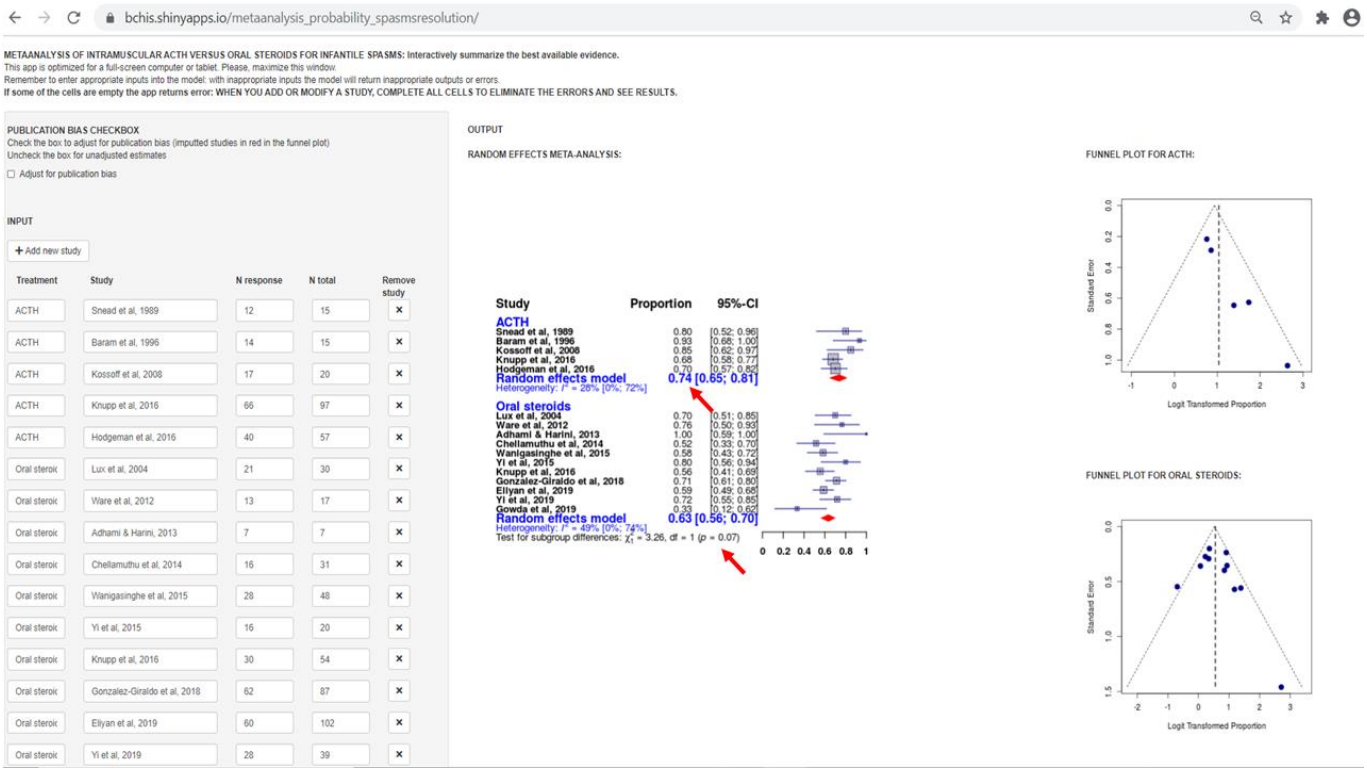


Analyses considering only studies with certain characteristics. If the reader considers only studies in which ACTH was natural (not synthetic) and only at a dose of 150 IU/m^2/day, the reader can go to https://bchis.shinyapps.io/metaanalysis_probability_spasmsresolution/

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, 1989 [3], Baram et al, 1996 [1], Kossoff et al, 2008 [4], and Knupp et al, 2016 [5] because these are the only studies with natural ACTH at 150 IU/m^2/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;97:375-379.
2. Wanigasinghe J, Arambepola C, Sri Ranganathan S, Sumanasena S, Attanapola G. Randomized, Single-Blind, Parallel Clinical Trial on Efficacy of Oral Prednisolone Versus Intramuscular Corticotropin on Immediate and Continued Spasm Control in West Syndrome. Pediatric neurology 2015;53:193-199.
3. Snead OC, 3rd, Benton JW, Jr., Hosey LC, et al. Treatment of infantile spasms with high-dose ACTH: efficacy and plasma levels of ACTH and cortisol. Neurology 1989;39:1027-1031.
4. 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;49:1504-1509.
5. Knupp KG, Coryell J, Nickels KC, et al. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol 2016;79:475-484.