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Negative randomized clinical trials (RCTs): further insight from the biostatistician's point of view

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Dear Editor,
Gattinoni and Giomarelli's [1] conclusion is that "negative" randomized controlled trials (RCTs) occur "...when they are too generic or wrong". However, I think that some insights have to be added from the biostatistician's point of view.

It is well known that RCTs are based on a null hypothesis (H_0) of no difference and on an alternative hypothesis (H_A) quantified on the "minimal clinical relevant difference (δ)" (superiority RCTs) or on the "maximal difference not clinically relevant" (non-inferiority and equivalence RCTs) or, better, for continuous variables, on the effect size: δ divided by the variability of the investigated phenomenon (σ). Then, after having fixed the significance level ($\alpha = 0.05$, two tailed, usually) and the pertinent statistical test, it is possible to calculate the sample size (to be reported in the paper [2]) for having a satisfactory

probability (power, 0.80, at least) of rejecting H_0 . Of course, if the H_A is true with a larger difference (effect size) than the foreseen one, the probability of rejecting H_0 will be greater and vice versa if the true difference (effect size) is lower.

Then, according to the frequentist approach [3], it is expected that, if the foreseen H_A is "true", it will be demonstrated in about the 80 % of the cases (power, correct rejection of a "false" H_0) and in the remaining about 20 % H_0 will not be disproved (β , type II error). Finally, the probability of wrongly rejecting a "true" H_0 (α , type I error) is equal to the fixed significance level (α).

A very frequent cause of "negative" RCTs is an overoptimistic H_A , often for having a lower number of patients to enrol into the RCTs; indeed, two "negative" trials (see references 8 and 10 in [1]) supposed a too high 20 % decrease of the mortality in favour of the prone position vs. the supine position.

Finally, it has to be said that researchers tend to wrongly interpret the significance value as the probability that the H_0 is "true" instead of, correctly, the probability of having obtained the result only by chance. In fact, in order to calculate the probability that H_0 is "true", one has to consider that the H_0 (and also the H_A) has "a priori" probability of being "true" ranging, in theory, from 0.00 to 1.00. So, by multiplying the "a priori" probability of a "true" H_0 by the "Bayes factor" that one can calculate from the significance p value [4, 5], it is possible to obtain the "a posteriori" probability of H_0 being

true. For example, statistically significant p values of 0.05 decrease the "a priori" probability of 0.05 (very unfavourable), 0.50 (equipose-like or toss-up) and 0.95 (very favourable) to about 0.013, 0.205 and 0.831, respectively. So, the probability of a significant result can be sensibly used to critically consider the probability that H_0 is actually "true".

Compliance with ethical standards

Conflicts of interest None.

References

1. Gattinoni L, Giomarelli P (2015) Acquiring knowledge in intensive care: merits and pitfalls of randomized controlled trials. *Intensive Care Med* 41:1460–1464. doi: [10.1007/s00134-015-3837-7](https://doi.org/10.1007/s00134-015-3837-7)
2. Schulz KF, Altman DG, Moher D, CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 152:1–7
3. Neyman J, Pearson ES (1933) On the problem of the most efficient tests of statistical hypotheses. *Philos Trans Roy Soc A* 231:289–337
4. Goodman SN (2001) Of P-values and Bayes: a modest proposal. *Epidemiology* 12:295–297
5. Goodman SN (1999) *Ann Intern Med* 130:1005–1013

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