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ORIGINAL ARTICLE

Clinical relevance of an intervention assessed by a meta-analysis of randomized clinical trials

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Abstract

Objectives: Many meta-analyses usually omit the number needed to treat, or perform the calculation incorrectly, despite its importance in clinical decision-making. Accordingly, we will explain in an easily understandable way how to perform this procedure to assess the clinical relevance of the intervention.

Study Design and Setting: The expressions of the Cochrane Library and the concepts of clinical relevance and evidence-based medicine were applied. Simple cutoff points were also established to facilitate the task of interpreting results. The method was applied to two published meta-analyses to illustrate its application to real cases (treatment nonadherence).

Results: In the first example, with a risk in the control group ranging from 0.22 to 0.70, sending mobile phone messages to remind chronic patients to take their medication is clinically relevant with a high degree of evidence. For the second example (single-pill regimen in patients suffering from hypertension and/or dyslipidemia after 6 months), the range of the assumed control risk was between 0.28 and 0.57.

Conclusion: The constructed algorithm could be applied to published meta-analyses or incorporated systematically in all meta-analyses with these characteristics.

Keywords: Number needed to treat; Meta-analysis as topic; Clinical trials as topic; Data interpretation; Statistical; Evidence-based medicine; Methods

1. Introduction

The results of a clinical trial are presented through the parameters: relative risk reduction (RRR), absolute risk reduction and number needed to treat (NNT), relative risk (RR), and odds ratio (OR) [1], although an intervention study usually reports its benefit based on the RR or the OR. The RR quantifies the relationship between the intervention and the event to be evaluated, determining how many times less risk of presenting the event the patients receiving the intervention have than the control group. However, its value may be the same for different clinical situations (different risks of unfavorable events may present the same RR), that is, it does not tell us in absolute terms the impact that the intervention would have in the population [1]. The OR is interpreted in a similar way to the RR [1], and with one of these two parameters, we can determine the other using the assumed control risk (ACR), that is, the risk of an unfavorable event in the control group [2,3].

The NNT (inverse of the absolute risk reduction) tells us the estimated number of patients that need to be treated with the intervention to prevent an unfavorable event compared with the control group. Although there is no consensus on which the NNT value is clinically relevant, cutoff points of 5, 10, 20, and 50 have been suggested to

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What is new?
Key findings

What this adds to what was known

- We propose a simple method to compute the NNT/RRR in a meta-analysis of RCTs.
- The method has been applied to two practical cases to facilitate its understanding.

What is the implication and what should change now

- By following our proposal, it is possible to determine the clinical relevance of an intervention.

classify the degree of evidence for the intervention, defining it as very high (<5), high (5–10), moderate (10–20), low (20–50), and very low (>50) [4]. However, the clinical relevance of an intervention goes beyond arithmetic calculations and is determined by clinical judgment, with the RRR being a useful measure in calculating clinical relevance. RRR values of 50% are almost always, and 25% frequently, considered clinically relevant regardless of statistical significance [5].

Despite the degree of evidence of a clinical trial when determining the effectiveness of an intervention, the trial is a single study conducted in a given population and period of time, so there could be differences in this effectiveness in different studies. This is where the meta-analysis of clinical trials plays a fundamental role as it combines the results of multiple scientific studies. In a meta-analysis, when the event to be evaluated is a binary variable, the RR or OR is generally provided, ignoring the calculation of the NNT or performing it incorrectly [6], despite its importance when making clinical decisions [1]. For this reason, the NNT should be presented taking into account the ACR, the time horizons in the improvement, and the confidence intervals (CIs) [6]. The Cochrane Library in its Handbook for Systematic Reviews of Interventions provides a series of indications for calculation of the NNT, whether an OR or an RR has been determined to assess the effectiveness of the intervention, indicating that the NNT should be given for a range of values for the ACR, bearing in mind that this may differ from the risk observed in the control group [7].

In the format of a tutorial, this article seeks to explain in an easily understandable way how to compute NNT and RRR values (only when OR is provided) in a meta-analysis of clinical trials for a range of ACR values, taking into account the cutoff points that define the level of evidence for NNTs and clinical relevance through the RRR [4,5]. To facilitate comprehension of the process, the method will be applied to a published meta-analysis [8], which assesses the effectiveness of a text message to decrease nonadherence in chronic patients. This example, developed in Results, consists of two parts. The first part concerns how to calculate the NNT with the meta-analysis selected [8], and the second part illustrates how to apply these results ourselves, as the value of the NNT depends on the ACR, as mentioned earlier. A second example has also been included in Supplemental Information 1 [9].

2. Methods

2.1. Meta-analysis of randomized clinical trials in which an odds ratio was calculated

The Cochrane Library indicates that we can obtain the NNT if we know the ACR value by applying the following expression [7]:

$$NNT = \frac{1}{\left| ACR - \frac{OR \cdot ACR}{1 - ACR + OR \cdot ACR} \right|}$$

Then, by applying this expression to the limits of the CIs, we obtain the CIs for the NNT [7]. Using the OR value, we can determine the RR [10]:

$$RR = \frac{OR}{1 - ACR + ACR \cdot OR}$$

Following the idea proposed by the Cochrane Library [7], we determine the CI for the RR. Finally, we calculate the RRR and its CI using the expression:

$$RRR = 100 \cdot (1 - RR)$$

2.2. Meta-analysis of randomized clinical trials in which a relative risk was calculated

When an RR is obtained in the study, we apply the following expression [7]:

$$NNT = \frac{1}{|ACR \cdot (1 - RR)|}$$

In addition, as in the previous case, we determine the CI. The RRR and its CI are obtained immediately, on determining the RR.

2.3. Plots to determine whether the intervention has high evidence for application in clinical practice

Now, because the NNT and the RRR (only when the meta-analysis reports the OR) are ACR functions, we proceed to substitute the ACR in the following set of values: $\{0.01 \cdot x: x=1,2,...,99\}$, that is, all possible ACR proportions rounded to two decimal places {0.1,0.2,0.3,...,0.97,0.98,0.99}, as this is the maximum precision a clinician has in determining effectiveness and makes the calculation much easier, although greater precision can be obtained. Extreme values are not included

(ACR = 0 or 1), as the NNT would not be defined for these values. This procedure is also applied to the CIs. Finally, we determine the ACR values that define an NNT of 5 and of 10, that is, those values that indicate that the intervention has high or very high evidence [4]. Next, for the RRR, we repeat the process, except that the cutoff points are 25% and 50% [5]. Evidently, when the meta-analysis calculates the RR, we know immediately whether the intervention has clinical relevance because we only need to assess the percentage obtained.

Once we obtain the cutoff points, we know the range of ACR values within which our intervention would be clinically relevant and have high or very high evidence, and we therefore know the benefit of its systematic implementation in clinical practice. By plotting the two graphs (NNT and RRR), we can determine the intersection of values that achieve high or very high evidence (NNT < 10) and are clinically relevant (RRR > 25%) [4,5]. When the ACR in the population of the clinician is at that intersection, the intervention would be of great benefit to his or her patients.

2.4. Assumed control risk in the population in question

We recommend that clinicians use their own data to determine the ACR, as data from the clinical trials included in the meta-analysis could be quite different. This is because participation in the trial could influence the placebo or Hawthorne effect and the risk of unfavorable events could vary [11,12], or there may simply be geographical variations, which would not correspond to the reality of the population under study. Should the clinician not have his or her own data, the ACR could be obtained through published observational studies conducted in geographical areas similar to the area studied, to carry out small pilot studies or to obtain population information through the analysis of electronic medical records, provided that it is a valid tool for the variable of interest.

2.5. Function to determine all the calculations in the algorithm

We have developed a function for the R software to perform the algorithm (Supplemental Information 2). This function will be illustrated in the second example.

3. Results

3.1. NNT calculation from a meta-analysis

In the proposed article that serves as an example [8], the meta-analysis obtains an OR of 2.107 (95% CI: 1.517–2.926) to determine treatment adherence. The first step is to invert the OR to assess the unfavorable event (nonadherence), obtaining: 0.475 (95% CI: 0.342–0.659). After applying the methodology described previously, we can see in Figs. 1 and 2 that the NNT is less than 10 (high evidence) for ACR values between 0.22 and 0.88 (Fig. 1) [4], whereas the intervention is clinically relevant (RRR > 25%) [5] when the ACR is less than 0.70. If we now intersect these two sets, we find that with an ACR ranging from 0.22 to 0.70, we have a clinically relevant intervention with high evidence. Within the context of the selected publication [8], if nonadherence ranges from 22% to 70% in our population of chronic patients, sending a message to their mobile phone as a reminder to take their medication would decrease nonadherence in a clinically relevant way in a median time of 12 weeks (range: 4-48 weeks).

3.2. Application of the calculated NNT to our setting

For instance, in the geographical area of the authors of the methodological article used as an example (Alicante, Spain), an observational study was published in 2014 that measured treatment nonadherence in a sample of 419 hypertensive patients [13]. This study found a magnitude of nonadherence of 62.8% based on tablet count [13], which would correspond to the ACR. Considering that this figure is in the range described previously, reminding patients to take their

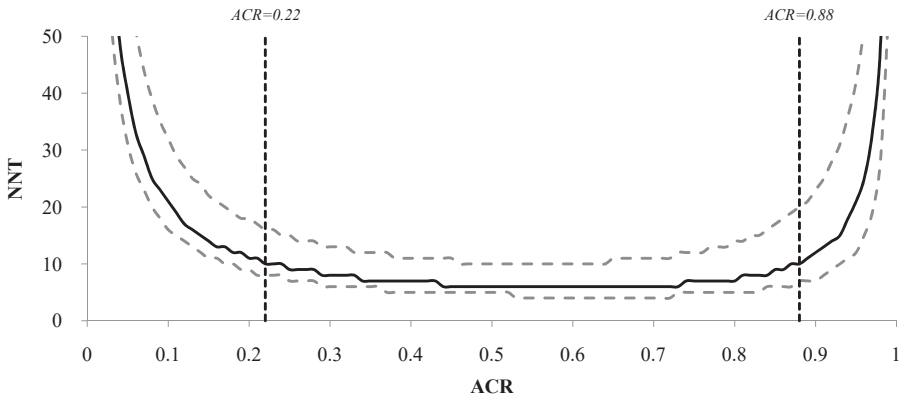

Fig. 1. Analysis of the number needed to treat depending on the assumed control risk. The two cut points indicate the ACR with NNT < 10. NNT, number needed to treat; ACR, assumed control risk.

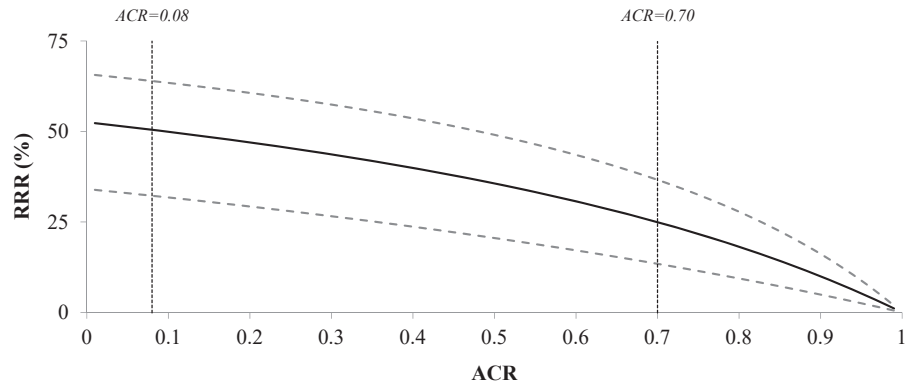

Fig. 2. Analysis of the relative risk reduction depending on the assumed control risk. The two cut points indicate the ACR with RRR = 25% and 50% (clinically relevant intervention). ACR, assumed control risk; RRR, relative risk reduction.

medication through mobile phone messages would be a clinically relevant intervention with high evidence.

3.3. Second example

We have applied the R script (Supplemental Information 2) to the second meta-analysis about a single-pill regimen in patients with hypertension and/or dyslipidemia [9]. The text is in Supplemental Information 1.

4. Discussion

4.1. Summary

This tutorial explains a method to calculate the NNT in a meta-analysis that has been or is due to be published. Two examples using real data are given to aid understanding of how to use the application.

4.2. Comparison with existing literature

Comparing our algorithm with other similar algorithms is difficult because, as far as we are aware, no studies have been published that include all the concepts assessed in this study with the aim of analyzing the NNT in a meta-analysis. Nonetheless, it should be noted that the methods applied in our algorithm correspond to those of the Cochrane Library and all we have done is join them systematically. This is like taking a mathematical formula developed on paper and putting it into a computerized form, as this latter just uses a formula that has been previously validated.

4.3. Implications to research and clinical practice

Most studies in the scientific literature fail to take into account the key points for the calculation of the NNT [6]. However, when the appropriate method is applied, the NNT provides important information that can be easily understood by clinicians to determine the benefit of an intervention for their patients. In the proposed algorithm, the expression provided by the Cochrane Library was applied [7], indicating a continuous range of values for the ACR, as suggested by this organization. In addition, the concepts of clinical relevance and some simple cutoff points for the NNT are incorporated, facilitating the task of interpreting results when classifying the degree of evidence of the intervention [4,5]. Finally, we would like to make several recommendations concerning the ACR because we believe that this value should be used in the population being studied as the main interest is in learning whether the intervention provides a benefit. This is an important point because if a value from the meta-analysis or from an isolated clinical trial is used, it would most likely not correspond to usual clinical practice, which is the real setting in which the intervention will be applied, whereas a clinical trial is controlled, and its conditions generally cannot be equated with clinical practice.

4.4. Limitations

We should bear in mind that this algorithm is applied to the results of the meta-analysis and does not assess other aspects of the review, such as the risk of bias or methodological quality [14,15]. These aspects must be analyzed before applying the algorithm described previously, as well as when interpreting the results of any systematic review. The example was selected solely for the purpose of illustrating the proposed method, and these aspects, which are generally studied in detail in systematic reviews of systematic reviews/meta-analyses, have not been assessed [15]. Finally, it is important to note that this algorithm can only be used if we have the information for the OR, its CIs, and the time horizon of the intervention. If the meta-analysis calculates the OR, these data should always be mentioned in the article. Indeed, we have yet to see a meta-analysis that failed to include them. Should this occur though, the authors could be contacted to obtain the missing information.

5. Conclusion

In this study, an algorithm was developed to evaluate the clinical relevance of an intervention based on the results of a meta-analysis of randomized clinical trials so that the reader can more easily understand this algorithm; it has been applied to two previously published meta-analyses to aid in replicating our methodology in other published meta-analyses. This algorithm may also be useful to authors when conducting a systematic review, as they could incorporate the techniques described here in their subsequent meta-analysis.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2020.12.010.

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