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Journal of Clinical Epidemiology 65 (2012) 863−868

Journal of Clinical Epidemiology

The "Lost NNT" can be used to represent uncertainty surrounding number needed to treat

Mohsen Sadatsafavi[a,b,*], Saeedreza Ganjizadeh[c], Rose Hatala[c], Carlo Marra[a], Mark FitzGerald[b,c]

[a]Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, BC, Canada V6T 1Z3

[b]Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Institute, 828 West 10th Avenue, Vancouver, BC, Canada V5Z 1M9

[c]Department of Medicine, University of British Columbia, 2775 Laurel Street, Vancouver, BC, Canada V5Z 1M9

Accepted 2 January 2012; Published online 30 May 2012

Abstract

Objectives: The uncertainty around number needed to treat (NNT) is often represented through a confidence interval (CI). However, it is not clear how the CI can help inform treatment decisions. We developed decision-theoretic measures of uncertainty for the NNT.

Study Design and Setting: We build our argument on the basis that a risk-neutral decision maker should always choose the treatment with the highest expected benefit, regardless of uncertainty. From this perspective, uncertainty can be seen as a source of "opportunity loss" owing to its associated chance of choosing the suboptimal treatment. Motivated from the concept of the expected value of perfect information (EVPI) in decision analysis, we quantify such opportunity loss and propose novel measures of uncertainty around the NNT: the Lost NNT and the Lost Opportunity Index (LOI).

Results: The Lost NNT is the quantification of the lost opportunity expressed on the same scale as the NNT. The LOI is a scale-free measure quantifying the loss in terms of the relative efficacy of treatment. We illustrate the method using a sample of published NNT values.

Conclusion: Decision-theoretic concepts have the potential to be applied in this context to provide measures of uncertainty that can have relevant implications.

Keywords: Number needed to treat; Value of information; Uncertainty; Bayesian statistics; Decision analysis; Confidence interval

1. Introduction

When deciding between two or more treatment options, decision makers (clinicians, patients, and policy makers) need to know the relative efficacy of treatments for the outcome of interest. There are several statistics to measure relative efficacy. Among them, the number needed to treat (NNT), that is, the number of patients who must be treated to achieve one favorable outcome (or to avoid one adverse outcome), is one of the most widely reported in medical decision-making literature [1]. The NNT, calculated as the reciprocal of the absolute risk reduction (ARR), was originally proposed by Laupacis et al. [2] as a measure for presenting the results of clinical trials with binary outcomes. It has since been extended for use with continuous outcomes [3] and survival data [4], and has led to closely related measures, such as the number needed to harm [5], number needed to screen [6], and the number needed to vaccinate [7].

In general, the NNT can be interpreted as quantifying the extra "effort" associated with the alternative treatment to achieve one outcome of interest. In Laupacis' words, "it tells clinicians and patients in more concrete terms how much effort they must expend to prevent one event" [2]. When the options in front of the decision maker are treatment vs. no treatment, the NNT helps illustrate that the treatment is costly and has potential adverse effects. When the NNT is being calculated for an alternative vs. a standard treatment, this is often because the alternative treatment is more effective but also more expensive and/or associated with a higher rate of adverse effects. In the context of the NNT, the term "effort" is loosely defined but can point to the time, labor, monetary costs, and patient risk that accompany any treatment.

Although Laupacis' definition of the NNT considers the treatment decision made by clinicians and patients, the NNT can equally be used in health policy decision making

* Corresponding author. Tel.: +1 604-822-9460; fax: 604-875-5179.
E-mail address: msafavi@mail.ubc.ca (M. Sadatsafavi).

0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2012.01.022

What is new?

Key finding

Currently, confidence interval is the standard way of communicating uncertainty around the number needed to treat (NNT). But the CI is not directly relevant to the treatment decision.

Uncertainty around treatment only matters because it may result in the choice of suboptimal treatment and hence causing an opportunity loss.

What this adds to what was known?

This article applies the principles of value of information analysis to the NNT context and provides two related measure of uncertainty: the Lost NNT and the Lost Opportunity Index (LOI).

What is the implication, what should change now?

Decision-analytic concepts can be applied to the NNT to provide measures of uncertainty that are more relevant to decision-making task than generic statistical measures of uncertainty like the CI.

The Lost NNT and LOI are especially applicable to population-level policy making on the adoption of competing treatment as they can help quantify the areas of greatest need for the investment of research fund

when the impact of decision at the population level (e.g., endorsing the coverage of a particular medication vs. another) is concerned [17]. For example, Heller et al. [8] proposed dividing the NNT by the proportion of the diseased population eligible for the intervention (disease impact number) and further by the proportion of the population with the disease of interest (population impact number) to provide a population perspective to the NNT [8,9].

One of the ways to use the NNT in making treatment decisions is to compare its value against a threshold NNT (NNT_T) [10], the point at which the effort and benefits are considered equal. In some situations, the choice of the NNT_T is obvious. For example, if treatments being compared differ only in their efficacy and are equal in all other respects, then the optimal treatment is the one that has the highest efficacy; in this case $NNT_T = \infty$ corresponding to ARR_T (treatment threshold on the ARR) of 0. In more complex situations, the NNT_T can be explicitly derived from the benefits, risks, and monetary costs associated with each treatment, and there are published methods on its calculation [11]. Even if such an objective threshold is not used, it has been argued that at the time of the decision, the NNT is being implicitly compared with an internal threshold based on subjective understanding of the risks, benefits, and preferences [12].

Furthermore, the NNT, like other indices estimated from sample data, is accompanied by sampling uncertainty. It is recommended that studies reporting NNTs always report confidence intervals (CI) as well [13]. Unfortunately, the NNT, as a reciprocal of the ARR, has some statistical disadvantages for calculating the CI when the ARR's CI crosses zero. In this situation, the bounds on the CI define an interval that contains infinity; these bounds therefore represent both the NNT and number needed to harm, and hence the CI does not have an intuitive interpretation [13,14].

2. The relevance of uncertainty in the NNT: the chance and consequences of making a wrong decision

The CI around the NNT communicates information about the degree of uncertainty around the value of the NNT, caused by the finite sample of the original studies reporting the ARR and the NNT. However, the question remains as to the practical relevance of such sampling uncertainty in medical decision making. It might be proposed that if the CI around the NNT contains the threshold NNT, the hypothesis that the alternative treatment is superior to the standard treatment is statistically rejected. Hence, the standard treatment remains the best option. But such hypothesis testing is inherently arbitrary (after all, why significance at the 5% level and not, say, 10%?) and is not necessarily in line with making the best treatment decision. (What if the underlying study was simply underpowered to detect a positive NNT?)

From a decision-theoretic viewpoint, the best treatment is the one that has the highest "expected" benefit [15]. An NNT that is below the NNT_T means the expected value of the efficacy of the alternative treatment is above the treatment threshold and hence is the treatment of choice, regardless of the statistical significance of difference between the NNT and the NNT_T or the CI around the NNT. Likewise, if the NNT is above the NNT_T, the standard treatment has the highest expected benefit and should be the treatment of choice. That is, it is the comparison between the point estimate of the NNT and the NNT_T that should influence the treatment decision, and statistical inference around the NNT is irrelevant for optimal decision making [15]. A decision maker who decides on the choice of treatment by comparing the NNT with the NNT_T will achieve the highest number of favorable outcomes per treatment decisions in the long run [15]. Following this argument, we developed indices that quantify and communicate such opportunity loss for the NNT.

3. The Lost NNT

The concept of the Lost NNT is analogous to the expected value of perfect information in health economics, which quantifies the opportunity loss because of not having perfect information in making a decision [16]. The calculation is