A closer look at the distribution of number needed to treat (NNT): a Bayesian approach

LEHANA THABANE

Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton ON, Canada
thabanl@mcmaster.ca

SUMMARY

In this paper, I present a Bayesian approach to estimation of the number needed to treat (NNT). The use of NNT as a measure of clinical benefit is now becoming commonplace. Various methods of estimation have been proposed, but none of them seem to provide entirely good estimates. Very little has been done to understand the statistical properties of NNT. Here, I derive the posterior distribution of NNT and use simulations to investigate the general behaviour of the distribution. The posterior mode of the distribution is proposed as a point estimate and results are compared with the conventional method of estimation of NNT done by inversion.

Keywords: Bayesian approach; Inverse Normal distribution; Number needed to treat; Posterior mode.

1. INTRODUCTION

Consider a clinical trial in which there are two arms: control and treatment. Suppose we have \( n_1 \) subjects allocated to the control group and \( n_2 \) subjects allocated to the treatment group. The objective is to compare the true risks \( p_1 \) and \( p_2 \), for the control and treatment groups respectively. The measure of reduction in risk is given by the difference \( p = p_1 - p_2 \). The number needed to treat is given by

\[
NNT = \frac{1}{|p_1 - p_2|} = \frac{1}{|p|},
\]

which can be interpreted as the expected number of subjects who must be treated to prevent one bad outcome, such as an adverse reaction or death, or to incur one additional bad outcome if \( p < 0 \). If there is no treatment effect, i.e. \( p = 0 \), then NNT is undefined (i.e. NNT=\( \infty \)).

The number needed to treat was introduced by Laupacis et al. (1988) as an alternative measure of expressing clinical benefit. Since its inception, NNT has gained great popularity and its use in clinical research is becoming commonplace: see for example Cook and Sackett (1995), Chatellier et al. (1996), Sackett (1996), Pickin and Nicholl (1995) and North (1995). While the measure has several attractive features over the traditional methods of expressing clinical results in terms of measures of relative efficacy such as relative risk and odds ratio, it has some undesirable properties (Lesaffre and Pledger, 1999; Altman, 1998; Bender, 2001). First, the fact that NNT is undefined (i.e. has singularity at \( p = 0 \)) presents a technical challenge in deriving and understanding the distribution of its estimators. Second, confidence intervals for NNT are hard to interpret for some intervals of \( p \) and sample sizes (Altman, 1998; Lesaffre and Pledger, 1999).

Newcombe (1999), Hutton (2000), Altman and Andersen (1999), among others, discuss statistical properties of NNT estimation. See also Cates (2002), Altman and Deeks (2002), and Moore et al. (2002),
for interesting debate on NNT, its role in meta-analysis and the connection to Simpson’s paradox. New analogous measures of NNT in the context of various designs and applications continue to emerge. For instance, most recently Walter (2001) defined new NNT-type measures for use with continuous and discrete data and explored the statistical properties of their respective estimators. Walter has also provided an account of examples of the diverse applications of NNT.

There are two major problems with conventional methods of estimating NNT: first, they are mostly based on inverting the estimate of the absolute difference \( p \) or its confidence interval. Using Jensen’s inequality (Berger, 1985, p. 40) one can easily illustrate that the inversion approach will lead to overestimation. Second, confidence intervals are often used as a way to incorporate our uncertainty in estimating NNT (Bender, 2001; Agresti and Caffo, 2000; Schouten, 2002). However, using confidence intervals often leads to inappropriate results which are hard to interpret (Altman, 1998). Lesaffre and Pledger (1999) are among the few that investigated the issue from a classical viewpoint using simulations.

The Bayesian approach seems to provide a good alternative by expressing the uncertainty about \( NNT \) via its posterior distribution. In this paper, I investigate the behaviour of NNT from a Bayesian viewpoint and propose a better estimate of NNT when there is efficacy or when the control treatment dominates the experimental.

In the next section, I derive the posterior distribution of NNT. Section 3 provides simulation results on the investigation of the behaviour of the distribution. Based on these results, the posterior mode is proposed as an estimate of NNT. Section 4 deals with discussion of the results.

2. THE POSTERIOR DISTRIBUTION OF NNT

Suppose we have \( x_1 \) and \( x_2 \) subjects with adverse reactions out of \( n_1 \) and \( n_2 \) respectively. Let \( D = (x_1, x_2, n_1, n_2) \) represent data from the trial. Assuming independent beta(\( \alpha_i, \beta_i \)) prior distributions for the \( p_i \) leads to the joint posterior distribution of \( (p_1, p_2) \) as a product of independent beta(\( x_i + \alpha_i, n_i - x_i + \beta_i \)) distributions (Bernardo and Smith, 1994; Berry, 1996; O’Hagan, 1996). Apart from mathematical tractability, beta priors offer great flexibility of distributional shape. Geisser (1984), Pham-Gia and Turkkan (1993), and Pham-Gia (1994) give detailed discussions on beta priors and the rationale for their use.

One can obtain the posterior distribution of the difference \( p = p_1 - p_2 \) (Pham-Gia, 1994) or that of \( NNT = 1/p \) by simple transformation, and using Markov chain Monte Carlo (MCMC) (Robert and Casella, 1999) to simulate directly from the posterior distributions. The posterior mean \( \mu_p \) and variance \( \sigma^2_p \) of \( p \) are respectively given by

\[
\mu_p = \mu_1 - \mu_2 \quad \text{and} \quad \sigma^2_p = \sum_{i=1}^{2} \frac{\mu_i (1 - \mu_i)}{n_i + \alpha_i + \beta_i + 1}
\]

with \( \mu_i = E(p_i|D) = (x_i + \alpha_i)/(n_i + \alpha_i + \beta_i) \) for \( i = 1, 2 \). Asymptotically, \( p \) will have a Normal posterior distribution with mean \( \mu_p \) and variance \( \sigma^2_p \). The common practice is to estimate NNT by \( 1/\mu_p \) and the corresponding interval estimate is given by the 95% credible interval \( (\mu_p \pm 1.96\sigma_p)^{-1} \).

Making the transformation to \( y = 1/p = NNT \), we find that the asymptotic distribution of \( Y \) is given by

\[
f(y|D) = \frac{1}{\sqrt{2\pi \sigma^2_p}} \exp \left\{ \frac{(1/y - \mu_p)^2}{2\sigma^2_p} \right\}.
\]

The density (2.1) is known as the inverse normal distribution (Johnson et al., 1995, p. 171). It is a special case of the generalized inverse normal family of density functions considered by Robert (1991). The mean
Fig. 1. Posterior distribution of NNT for A: $\mu_p = -0.1, 0.1; \, \sigma_p = \sqrt{1/12}$; B: $\mu_p = -0.04, 0.04, \, \sigma_p = \sqrt{1/12}$; C: $\mu_p = -0.02, 0.02, \, \sigma_p = 0.009$. The dashed and thick lines represent negative and positive $\mu_p$ values respectively.

and variance of the distribution (2.1) do not exist. However, the distribution has two modes at

\[
\hat{NNT}_1 = -\frac{\mu_p + \sqrt{\mu_p^2 + 8\sigma_p^2}}{4\sigma_p^2} \quad \text{and} \quad \hat{NNT}_2 = \frac{\sqrt{\mu_p^2 + 8\sigma_p^2} - \mu_p}{4\sigma_p^2}.
\] (2.2)

Thus the point estimate of NNT would be given by $\hat{NNT}_2$ when there is efficacy and by $\hat{NNT}_1$ when the control treatment dominates the experimental. Figure 1 shows graphs of (2.1) for different values of $\mu_p$ and $\sigma_p$. We observe from Figure 1 that the pdf based on $\mu_p < 0$ is a mirror image of that of $\mu_p > 0$.

Adopting the Bayesian approach has several advantages: firstly, the posterior distribution could be used to calculate other quantities of interest such as expected utilities or losses needed for optimal decisions. Further, posterior probabilities can be used to guide clinical decisions. Note also that one can use MCMC methods to sample from the exact posterior distribution of $NNT$. In short, Bayesian methods are well suited for modelling data in healthcare research where decision making is the most important objective. For a discussion on the advantages of Bayesian techniques in healthcare research, see for example Wingler (2001) and Hornberger (2001).
3. A SIMULATION STUDY

Simulations were performed to study the behaviour of the posterior distribution of $NNT$ and to compare the estimates of $NNT$ based on the Bayesian approach and on the usual approach of inverting the estimate of $p$. The details of the simulation results are available at http://www.biostatistics.oupjournals.org/NNTsim.pdf. In general, the results show that while the posterior distribution of $p$ is nicely symmetric, that of $NNT$ is not. Comparisons of the estimates of $NNT$ indicate that the posterior mode consistently gives the least average error percentages and outperforms conventional estimators if the support of the distribution lies entirely in the positive range, i.e. if the posterior probability of negative $NNT$ is zero or very close to zero.

4. DISCUSSION

As a measure of clinical benefit, $NNT$ is intuitively attractive due to its interpretability in a clinical setting. The Bayesian approach provides a constructive alternative to classical methods to express the uncertainty about $NNT$ using its posterior distribution, although in some cases the distribution has unpleasant properties because of the obvious instability of $NNT$ as an estimand. When the posterior distribution of $NNT$ lies entirely in the positive range of the axis, I propose the posterior mode of the distribution of $NNT$ as an estimator. Simulations to compare this estimator with the classical estimator and another Bayesian ‘estimator’ obtained by inverting the posterior mean of $p$ show that the posterior mode outperforms its two counterparts with respect to the average error percentage. I recommend some caution when using estimates of $NNT$ as a measure of clinical benefit. Efficacy or clinical effect first has to be established, and one needs to check whether the support of the posterior distribution lies entirely in the positive range. Estimation of $NNT$ for the case where there is non-zero posterior probability that $p < 0$, and the actual posterior distribution is bi-modal, is still under investigation.

ACKNOWLEDGEMENTS

This research was partly supported by the Natural Sciences and Engineering Research Council, Grant # RGPIN 227331-200. Special thanks to Dr Charlie Goldsmith for his guidance and valuable input on preliminary versions of the paper. I also wish to thank Drs Andy Willan and Stephen Walter for their input. Thanks are due to the editor and referee for helpful comments and suggestions which improved the presentation significantly.

REFERENCES


PICKIN, M. AND NICHOLL, J. (1995). Number who benefit per unit of treatment may be a more appropriate measure. British Medical Journal 310, 1270.


SCHOUTEN, H. J. A. (23). Simple and effective confidence intervals for the number needed to treat. Controlled Clinical Trials 100, 102.


[Received June 17, 2002; first revision August 20, 2002; second revision October 4, 2000; third revision October 23, 2002; accepted for publication November 4, 2002]