ALL DRESSED UP AND KNOW WHERE TO GO: AN EXAMPLE OF HOW TO USE NET BENEFIT REGRESSION TO DO A COST-EFFECTIVENESS ANALYSIS WITH PERSON-LEVEL DATA (THE 'A' IN CEA)

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Abstract

The objective of this paper is to show how to use person-level cost and outcome data to do a cost-effectiveness analysis using net benefit regression. With a small data set (from a hypothetical clinical trial of a new pharmacologic treatment for schizophrenia), we show how to use simple regression techniques to do a cost-effectiveness analysis. The method for the economic analysis that we illustrate is called net benefit regression. The first step is to create a net benefit variable (using each patient's cost and outcome data). The second step is to do regression. This simple process for the analysis of cost-effectiveness data using regression tools allows additional insight and the potential to implement more advanced techniques.

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Introduction

We live in an era where clinical freedom is being challenged in many ways. With the introduction of evidence-based medicine, suppliers and providers of treatment have been asked to consider whether there exists evidence that their recommended treatment works. A sad realisation from this process has been that scarcity of resources prevents the provision of all treatments that do work. Decision makers wrestle with the problem of how to spend their limited resources. How should we decide what treatments to cover? Drummond et al. (2005) have noted that, "methods such as 'what we did last time', 'gut feelings' and even 'educated guesses' are not always better than organised consideration of the factors involved in a decision to commit resources to one use instead of another." Decision makers throughout the world have started to embrace economic evaluations, like cost-effectiveness analysis, as a way of structuring an organised consideration of the tradeoffs related to the extra benefits and extra costs of a new treatment. With the ascendancy of economic evaluation as a key part of many countries' decision-making process about whether to pay for a new treatment, the main focus has shifted from "Does the new treatment work?" to "Is the new treatment worth it?" To answer this question, one must simultaneously consider the new treatment's additional costs in relation to its additional benefits.

High quality economic evidence about mental health treatments and interventions is not abundant. Evers et al. (1997) reviewed the quality of economic evaluation in mental health care and found "few good full economic evaluation studies have been undertaken in the domain of mental health care." Six of the 91 studies that were reviewed (about 7%) reported additional costs and effects. Without this information, one cannot compare the additional costs to the additional benefits. Even once the correct data have been collected, there may still be challenges. For example, a review of all economic evaluations published in 2003 found "a substantial number of clinical trial-based economic studies using statistical methods of poor quality" (Doshi et al. 2006). Complacency about this type of "technical" finding can have important repercussions. For example, *in spite of published claims to the contrary*, "currently there is no clear evidence that atypical antipsychotics generate cost savings or are cost-effective in general use among all schizophrenia patients" (Polsky et al. 2006). This was the conclusion of a recent review of economic evaluations of second generation antipsychotics. The

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studies' claims of cost-effectiveness were invalidated by methodological problems; however, it is unlikely that any treatment will be cost-effective for *all* patients with a particular type of mental illness.

Methodological commentators have suggested that some of the limitations in economic evaluation methods may be because "the advances in design and statistical techniques for the analysis of cost and cost-effectiveness are published in highly technical economics or biostatistical journals" (Polsky et al. 2006). This highlights the importance of a type of knowledge exchange where fundamental economic evaluation methods are explained in an understandable way to a wider audience. The objective of this paper is to provide a step by step example introducing how to analyse patient-level cost and effect data to produce a high quality cost-effectiveness analysis using net benefit regression. After briefly explaining what cost-effectiveness analysis is and how it is done, we illustrate our main points using hypothetical data from a clinical trial of a new pharmacologic treatment for schizophrenia. Because the data are reproduced in their entirety in the paper, interested readers can follow along, checking to see if their results and conclusions match those we report at the end of this paper.

Methods

Background on cost-effectiveness analysis

There are many different types of economic evaluations, with cost-effectiveness analysis being one of the most popular (Hoch and Dewa 2003). In a cost-effectiveness analysis (CEA), the goal is to estimate the extra cost and the extra effect of a new treatment relative to a comparator. To answer the question "Is treatment cost-effective?" one must do the following: first, estimate the extra cost (ΔC); second, estimate the extra effect (ΔE); third, compute the extra cost per extra effect (ΔC/ΔE); and fourth, judge whether the trade-off estimated in step 3 is "worth it". A new treatment is cost-effective if the value of ΔE is greater than ΔC. For example, patients treated with a new drug may enjoy 2 more weeks symptom-free on average; however, patients taking this new drug may experience €850 more in costs compared to patients treated with usual care. The extra cost for one more unit of patient outcome is €425 per symptom-free week (ΔC/ΔE = €850 more in costs / 2 more symptom-free weeks). Is this a good deal?

Economics states that a good deal is one in which you value what you get more than what it costs you. If we as a society value each additional symptom-free week at €500, then paying €425 per symptom-free week represents a good deal. When our estimate of the extra cost for one more patient outcome (ΔC/ΔE) is less than society's willingness to pay for one more patient outcome, the new treatment is cost-effective. In our example, the *value* of the additional patient outcome equals 2 (*i.e.*, ΔE or how many additional units of patient outcome were obtained) times €500 (*i.e.*, willingness to pay or how much each unit is worth). When we are willing to pay €500 for each symptom-free week, creating 2 symptom-free weeks is worth €1,000 (*i.e.*, 2 x €500). The additional cost to create €1,000 worth of patient outcome was €850 (since ΔC = €850). The incremental net benefit of the new treatment is €150 (since €1,000 - €850 = €150) when willingness to pay (WTP) is €500.

Background on incremental net benefit

In general, incremental net benefit (ΔNB) equals WTP x ΔE - ΔC. When ΔNB > 0, that means the value of the extra patient outcome created (WTP x ΔE) was greater than the extra costs (ΔC). In other words, when ΔNB > 0, a new treatment is cost-effective. When ΔNB < 0, a new treatment is not cost-effective since the extra costs outweigh the extra benefits (*i.e.*, ΔC > WTP x ΔE). Of course, the key question is "What value should be used for willingness to pay?" Typically, CEAs use a variety of WTP values to see how sensitive the results are to assumptions about WTP.

There are a variety of ways to obtain an estimate of ΔNB. For example, one could compute ΔE and ΔC separately, and then use them with a WTP value to compute ΔNB = (WTP x ΔE) - ΔC. The estimate of ΔE is made from the difference in average effect estimates for new treatment and a comparator (e.g., standard or usual care). That is,

$\Delta E = \text{Average Effect}_{\text{new treatment}} - \text{Average Effect}_{\text{usual treatment}}$.

Similarly, the estimate of ΔC comes from the difference in the average cost estimates

$\Delta C = \text{Average Cost}_{\text{new treatment}} - \text{Average Cost}_{\text{usual treatment}}$.

Commonly, the sample means are used as estimates of the Average Effects and Average Costs for new and usual treatment. Alternatively, the estimates of ΔE and ΔC can be generated using regression (Hoch and Smith 2006). An estimate for ΔNB can also be made using regression methods.

Net benefit regression

Hoch et al. (2002) introduced net benefit regression as a way to estimate ΔNB using regression methods. The main idea from that paper comes from the observation that when running a regression like

$$Y = \beta_0 + \beta_1 tx,$$

where $tx = 0$ if the patient received usual care and 1 if the patient received new treatment, then the estimate of β_1

$= \text{Average Y}_{\text{new treatment}} - \text{Average Y}_{\text{usual treatment}}$.

Therefore if the dependent variable (Y) is Cost, then the estimate of β_1

$= \text{Average Cost}_{\text{new treatment}} - \text{Average Cost}_{\text{usual treatment}} = \Delta C$,

and if the dependent variable (Y) is Effect, then the estimate of β_1

$= \text{Average Effect}_{\text{new treatment}} - \text{Average Effect}_{\text{usual treatment}} = \Delta E$.

The authors show that if the dependent variable is WTP x Effect - Cost, then the estimate of β_1

$= \text{Average NB}_{\text{new treatment}} - \text{Average NB}_{\text{usual treatment}} = \Delta NB$.

The reason that this is an important observation is that if one creates a net benefit variable for each patient (*i.e.*, computing WTP x effect – cost for each person) and then runs the regression,

$$NB = \beta_0 + \beta_1 tx,$$

where *tx* is defined as before, the coefficient estimate

for β_1 equals ΔNB (the incremental net benefit of the new treatment). If the estimate of $\beta_1 > 0$, the new treatment is cost-effective. The estimate of β_1 changes as the choice of WTP changes. Therefore, it is a good idea to run a few net benefit regressions with different WTP values to see how sensitive the results are to the choices of WTP. In the next section, we illustrate how the process works and how to interpret the results.

Data

To illustrate how to perform a CEA using net benefit regression, we present data from a hypothetical 6-week clinical trial comparing novel drug therapy (*tx* = 1) to novel talk therapy (*tx* = 0) for people with schizophrenia. We have made up a data set with 8 people to facilitate the duplication of our methods and reasoning. The data, presented in **Table 1**, show that there was heterogeneity in the severity of the patients' disease. From the rightmost column, it is clear that half of the sample had what could be classified as "severe" schizophrenia and half did not. The patient outcome chosen to represent "success" was symptom-free weeks.

Table 2 shows the calculation of each person's net benefit variable using low (€10), medium (€100) and high (€1,000) WTP values. The data for a net benefit regression are then presented in **Table 3** and illustrated in **Figure 1**. The subsequent tables and figures show results created using STATA version 9.

The results of the first regression we ran are not reported, but the mistakes are. When we estimated the regression

$$nb1000 = \beta_0 + \beta_1\, tx,$$

we plotted the regression residuals (*i.e.*, the differences between the true *nb1000* and what the regression predicted *nb1000* to be). This is standard practice because a regression model is not supposed to make systematic errors. **Figure 2** shows that for patients who were not severe, the model under-predicts the net benefit of talk therapy (*i.e.*, has positive residuals) but for patients who were severe, the model over-predicts the net benefits of talk therapy (*i.e.*, has negative residuals). **Figure 2** shows the opposite story for drug therapy; the model is under-predicting net benefits for patients who are not severe but over-predicting net benefits for patients who are severe. Because the regression diagnostics show the model is making systematic mistakes, it suggests we may need separate models for patients depending on their disease severity.[1]

Thus, we report stratified regression results. **Figure 3** illustrates detailed results from one net benefit regression and **Table 4** summarises all of our results. In general, the models for non-severe patients tend to report ΔNB estimates (the coefficient on *tx*) that are negative and not statistically significant, while the models for severe patients tend to report ΔNB estimates that are positive and statistically significant.

Results

Table 1. *Patient-level data and variables definitions (variable name)*

Patient Number (*idno*)	Patient outcome at 6 weeks (*effect*)	Patient costs at 6 week (*cost*)	Treatment strategy (*tx*)	Disease type (*dztype*)
1	3 weeks symptom free	€ 8 500	Novel talk therapy (*tx* = 0)	Severe disease (*dztype* = 1)
2	4 weeks symptom free	€ 8 000	Novel talk therapy (*tx* = 0)	Not severe disease (*dztype* = 0)
3	4 weeks symptom free	€ 9 000	Novel talk therapy (*tx* = 0)	Severe disease (*dztype* = 1)
4	6 weeks symptom free	€ 7 000	Novel talk therapy (*tx* = 0)	Not severe disease (*dztype* = 0)
⇧ Patients receiving talk therapy ⇧ ⇩ Patients receiving drug therapy ⇩				
5	3 weeks symptom free	€ 8 000	Novel drug therapy (*tx* = 1)	Not severe disease (*dztype* = 0)
6	5 weeks symptom free	€ 10 000	Novel drug therapy (*tx* = 1)	Not severe disease (*dztype* = 0)
7	5 weeks symptom free	€ 7 800	Novel drug therapy (*tx* = 1)	Severe disease (*dztype* = 1)
8	6 weeks symptom free	€ 8 000	Novel drug therapy (*tx* = 1)	Severe disease (*dztype* = 1)

[1] It is possible to use interaction terms in this case - and they are computed in Table 3 - however, we feel it eases the exposition to do a stratified analysis by disease type. Hoch and Smith (2006) discuss how to handle a continuous variable that may affect the cost-effectiveness of a new treatment, and Hoch et al. (2002) discuss how to handle a variety of variables in this context.

Table 2. *Calculating patient-level net benefit using patient-level cost and effect data, by size of willingness to pay for one more patient outcome*

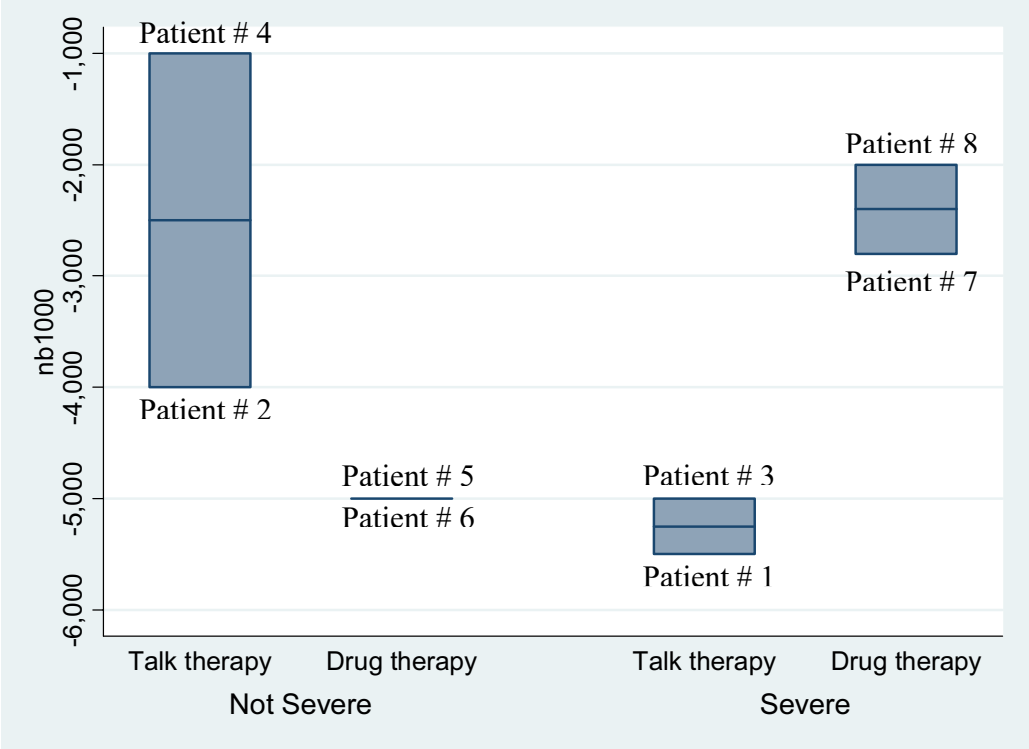
	Person identification number								
Willingness to pay value	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**
€ 10	**€ 10** · 3 – € 8 500 – € 8 470	**€ 10** · 4 – € 8 000 – € 7 960	**€ 10** · 4 – € 9 000 – € 8 960	**€ 10** · 6 – € 7 000 – € 6 940	⇦ Talk therapy ⇦ ⇨ Drug therapy ⇨	**€ 10** · 3 – € 8 000 – € 7 970	**€ 10** · 5 – € 10 000 – € 9 950	**€ 10** · 5 – € 7 800 – € 7 750	**€ 10** · 6 – € 8 000 – € 7 940
€ 100	**€ 100** · 3 – € 8 500 – € 8 200	**€ 100** · 4 – € 8 000 – € 7 600	**€ 100** · 4 – € 9 000 – € 8 600	**€ 100** · 6 – € 7 000 – € 6 400		**€ 100** · 3 – € 8 000 – € 7 700	**€ 100** · 5 – € 10 000 – € 9 500	**€ 100** · 5 – € 7 800 – € 7 300	**€ 100** · 6 – € 8 000 – € 7 400
€ 1 000	**€ 1 000** · 3 – € 8 500 – € 5 500	**€ 1 000** · 4 – € 8 000 – € 4 000	**€ 1 000** · 4 – € 9 000 – € 5 000	**€ 1 000** · 6 – € 7 000 – € 1 000		**€ 1 000** · 3 – € 8 000 – € 5 000	**€ 1 000** · 5 – € 10 000 – € 5 000	**€ 1 000** · 5 – € 7 800 – € 2 800	**€ 1 000** · 6 – € 8 000 – € 2 000

Table 3. *Data used in the net benefit regression**

Patients	**Dependent variables**			**Independent variables**		
idno	*nb10***	*nb100***	*nb1000***	*tx*	*dztype*	*tx × dxtype*
1	-8470	-8200	-5500	0	1	0
2	-7960	-7600	-4000	0	0	0
3	-8960	-8600	-5000	0	1	0
4	-6940	-6400	-1000	0	0	0
⇧ Patients receiving talk therapy ⇧ ⇩ Patients receiving drug therapy ⇩						
5	-7970	-7700	-5000	1	0	0
6	-9950	-9500	-5000	1	0	0
7	-7750	-7300	-2800	1	1	1
8	-7940	-7400	-2000	1	1	1

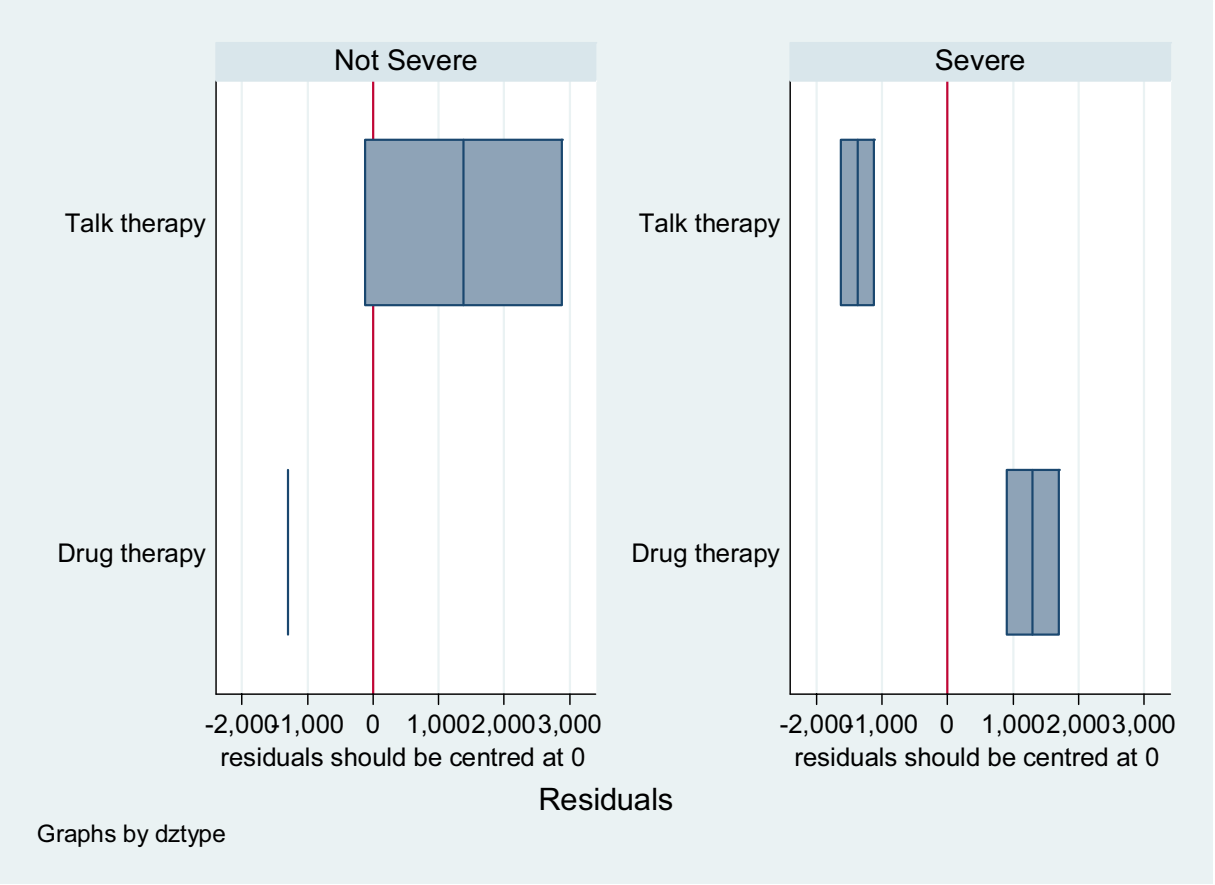
* The relevant data from Table 3 related to *nb1000* are plotted in Figure 1
** The net benefit variables are named to reflect the willingness to pay value that was used in their creation. For example, *nb1000* uses a willingness to pay of €1 000.

Figure 1. *Net benefit with willingness to pay = € 1 000, by disease type and treatment therapy*



Box plots, such as the one above, use the line bisecting the middle of the box to indicate the median. Since there are only two patients in each therapy/disease group, the median line in the middle of each box also indicates the mean of the net benefit data for each therapy/disease group. Also, because there are only two patients in each therapy/disease group, the upper and lower limits of the boxes represent the data for each of the two patients in that category. In the scenario where both "not severe" patients taking drug therapy (patients #5 and #6) have the same data, the upper and lower limits are the same.

Figure 2. *Box plots of the regression residuals for nb1000 = β_0 + β_1 tx by disease severity and treatment option*



Since there are only two patients in each therapy/disease group, the median line in the middle of each box indicates both the median and the mean. Also, because there are only two patients in each therapy/disease group, the upper and lower limits of the boxes represent the data for each of the two patients in that category. In the scenario where both "not severe" patients taking drug therapy have the same data, the upper and lower limits are the same.

Discussion

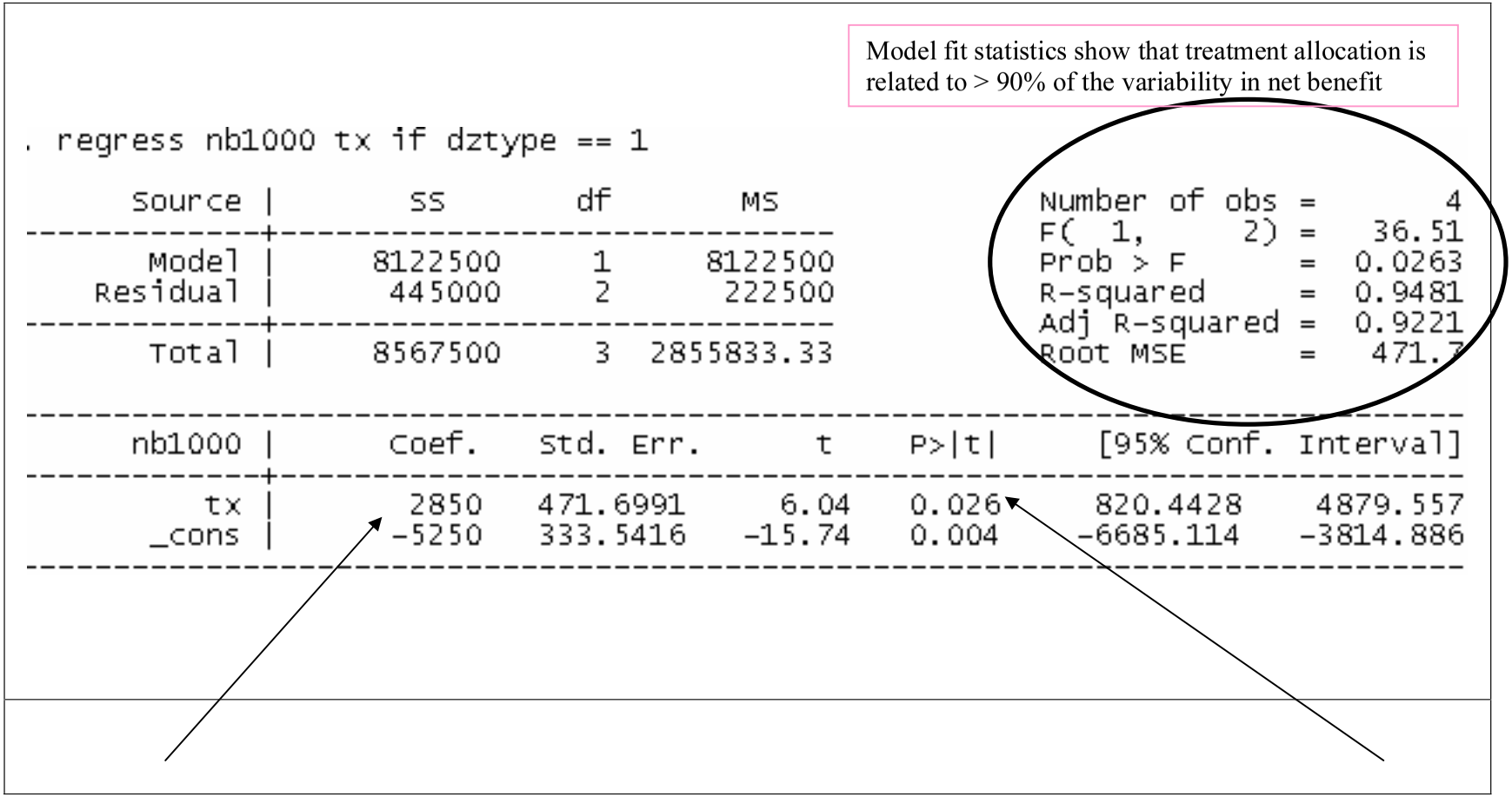
In the illustrative example, the hypothetical new drug treatment does not appear to be cost-effective among patients who do not have severe disease. All of the regression estimates show that the extra benefits are outweighed by the extra costs by anywhere from about €1,500 to €2,500, depending on what WTP value is used (this is based on the *tx* row in **Table 4**). In contrast, in the net benefit regression models for severe patients, the drug treatment appears to be cost-effective. The extra benefits are estimated to outweigh the extra costs by €870 to €2,850, depending on what WTP value is used. Moreover, statistical significance is achieved at higher WTP values.[2]

Separate models were fitted because the assumptions for regression did not appear to hold. Many assumptions for regression can be verified visually (*e.g.*, examining regression residuals for patterns). Another benefit of regression is that model fit statistics are reported. These provide context about how well the variables in the model pick up variation in the cost-effectiveness of a new treatment. An additional strength of net benefit regression is that it allows more advanced regression-based methods to be incorporated naturally (*e.g.*, hierarchical models, propensity scores, *etc.*).

In the end, we are still left with the question of what WTP to use. If the value of WTP does not affect the results, the issue is not a contentious one. If, however, the sign of the ΔNB depends on the WTP, this information is still useful. According to Williams (1992), "one of the advantages of a systematic cost-effectiveness analysis is that it… requires explicit judgments to be made… [which] should have the important… benefit of improving the accountability of policy-makers to the community they are serving". The

[2] The p-value is not always the right quantity to use when quantifying statistical uncertainty about ΔNB. Articles by Fenwick et al. (2006) and Hoch et al. (2006) provide additional details.

Figure 3. *How to read the output from a net benefit regression with willingness to pay = € 1 000, for patients with severe disease type (dztype = 1)*



The coefficient estimate on *tx* is > 0 (showing that extra benefits are worth €2 850 more than extra costs); this estimate is significant in a statistical sense ($p < 0.03$). Results for a variety of willingness to pay values are reported in Table 4. The last column of Table 4 summarizes the findings reported here in Figure 3. The 95% confidence intervals appear in the last two columns of Figure 3.

Table 4. *Net benefit regression results with hypothetical data from Table 1*

	Willingness to pay = € 10		Willingness to pay = € 100		Willingness to pay = € 1 000	
Variables	*Not severe Disease*	*Severe Disease*	*Not severe Disease*	*Severe Disease*	*Not severe Disease*	*Severe Disease*
Constant Term	-7 450*	-8 715***	-7 000*	-8 400***	-2 500	-5 250**
Tx	-1 510	870	-1 600	1 050*	-2 500	2 850*
Model Fit Statistics						
Adjusted R^2	0.022	0.077	0.028	0.89	0.37	0.92
F (df)	1.84 (1, 2)	10.96 (1, 2)	2.19 (1, 2)	25.94* (1, 2)	2.78 (1, 2)	36.51* (1, 2)

* $p < 0.05$. ** $p < 0.01$. *** $p < .001$

net benefit approach focuses attention on WTP. Analysts may suggest WTP values from the scientific literature, previous recommendations or past decisions, but it is not clear that these unsolicited opinions are warranted. Even among the same group in the same country deciding on the WTP to pay for the same patient outcome, context appears to matter (Devlin and Parkin 2004, George et al. 2001). Thus, it is not clear that WTP values are or should be a "one size fits all" matter. Even if there were some magic WTP that were always the right number to use, it would not come from clinical trial data. The person-level data that are analysed in the cost-effectiveness analysis are cost and outcome data. WTP values do not come from one's data; they come from one's values. Economic evaluation is simply one component of the decision making process. It is best used as "a way of organising thought rather than as a substitute for it" (Drummond et al. 2005).

Summary

Decision makers have embraced economic evaluations to inform decisions about which treatments will be covered and which will not. There is a role in this persuasion process for cost-effectiveness analysis with patient-level data. Patient-level data are often available from a clinical trial or an administrative data set. By linking "prices" to service use data and combining this with patient outcome data, one can create cost and effect data suitable for economic analysis. The goal of a cost-effectiveness analysis is to quantify the trade-off between resources used and outcomes gained.[3] Net benefit regression can assist in this analysis by providing a natural link to regression tools.

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[3] CEA determines the relative efficiency of a treatment alternative, while cost-benefit analysis assesses whether a treatment is worthwhile. This point is illustrated in our hypothetical example where both treatment options are "bad" ideas (i.e., both have negative net benefits) but one of them is less "bad".