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What is an NNT?

- **The number needed to treat (NNT)** has become a popular **measure of effectiveness of interventions.** NNTs are much easier to comprehend than any statistical description, and NNTs for different agents can be easily compared.

- An NNT is **treatment-specific** and describes the difference between a treatment and a control in achieving a particular clinical outcome. It can be used to describe any outcome where event rates are available for both a treatment and a control.

- Clearly defining a useful clinical outcome is the best way of calculating and using NNTs.

- **NNTs calculated from systematic reviews of randomised controlled trials provide the highest level of evidence** because systematic reviews contain all the relevant information and the largest numbers of patients available for analysis.

- **NNTs only have utility when the evidence** on which they are based **fulfils criteria of quality, validity and size.** Even data from a systematic review can be compromised.

- An NNT is just one part of the information required in making a purchasing decision. There are many other factors, including adverse effects, costs, and individual, social and medical priorities.

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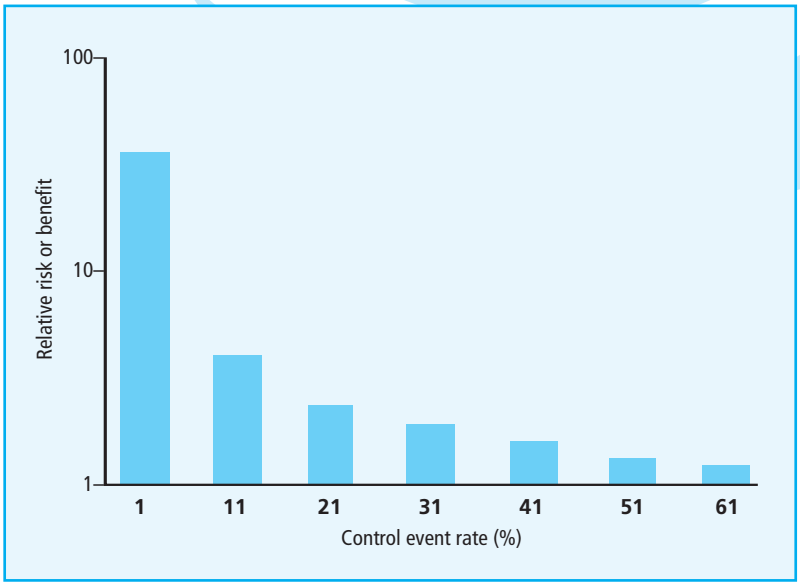
Rationale for using NNTs

Why would you want to use something like a **number needed to treat (NNT)** and complicate the nice statistics – such as relative risks (RRs) and odds ratios (ORs) – we usually get from clinical trials and meta-analyses? The trouble is that RRs, for instance, depend much more on what happens with a control than with a treatment.

Look at Figure 1. In this hypothetical example of a series of trials, we use the same absolute effect – a 30% benefit with treatment – but vary the event rate for the control group from 1% to 61%; and, yes, control event rates this high do occur in some circumstances, and occur frequently in small trials, because of the random play of chance. You can see that the RR varies massively, from over 30 to just over 1.5; however, the same absolute benefit is given, with an extra 30% of patients benefiting in each case, and in each case the NNT is 3.3.

Now look at Table 1, which shows how the NNT varies with the absolute risk increase (the percentage of patients benefiting because of the treatment). In each of these trials, the RR is the same, yet the proportion of patients benefiting from treatment varies from 1% to 44%.

Figure 1. Variation of relative risk with control event rate



Of course we need statistical outcomes to tell us whether a result is statistically significant, using well-tried, formal tests of significance; however, we need to go further than this because the statistical result is not helpful in making clinical practice decisions. Here the **NNT** (or **NNT to prevent [NNTp],** or **number needed to harm [NNH]** – see below) **can help to identify the proportion of patients likely to have treatment-specific effects.**

The **best NNT** is **1,** when everyone experiences benefit with the treatment and no one with the control. The **worst NNT** is **–1,** when everyone experiences benefit with the control and no one with the treatment. Between these two extremes, NNT values increase to infinity, when there is no difference between treatment and control.

NNTs as a measure of effectiveness

Treatment specificity

An NNT is treatment-specific. It describes the difference between active treatment and control in achieving a particular clinical outcome.

An **NNT of 1** means that a **favourable outcome** occurs **in every patient given the treatment** and **in no patient in a comparison group** – the 'perfect' result in, say, a therapeutic trial comparing an antibiotic with a placebo, such as in the eradication of *Helicobacter pylori* infection (Table 2).[1,2]

Studies of treatments usually involve big effects in (relatively) small numbers of patients and, therefore, may have 'better' NNTs than those of prophylactic interventions. There are no set limits for NNTs to be considered clinically effective, but it is generally considered that the lower the NNT (the closer to 1), the better.

A correctly defined NNT must always specify the comparator, the therapeutic outcome, the duration of treatment necessary to achieve that outcome and the 95% confidence interval (CI).

Table 1. Six hypothetical trials showing variation of NNT with absolute event rates*

Trial	Number of patients with outcome		EER (%)	CER (%)	RR	AR increase (%)	NNT
	Active	Placebo					
1	800	360	80	36	2.2	44	2.3
2	400	180	40	18	2.2	22	4.6
3	200	90	20	9	2.2	11	9.1
4	100	45	10	5	2.2	5	18.2
5	50	23	5	2	2.2	3	37.0
6	20	9	2	1	2.2	1	90.9

* Trials with 1,000 patients each given active treatment or placebo

AR: absolute risk; CER: control event rate; EER: experimental event rate; NNT: number needed to treat; RR: relative risk

Calculating an NNT

The NNT can be calculated from the simple formula:

$$\text{NNT} = \frac{1}{\text{(proportion benefiting from experimental intervention)} - \text{(proportion benefiting from a control intervention)}}$$

A fuller mathematical description is given in Box 1.

For prophylaxis, where fewer events occur in the treated group, the **calculation** shown **will produce negative NNTs.** You can use those numbers by simply ignoring the sign (the numbers will still be correct), or you can switch the active and control groups around to provide NNTs with a positive sign.

NNTs can also be calculated from statistical outputs of clinical trials or systematic reviews, from ORs and from the relative risk reduction (RRR) – see the 'Further reading' section below for more information on these statistical measures.

There is no absolute value for an NNT that defines whether something is effective or not. NNTs for treatments are usually low because we expect large effects in small numbers of people. Since few treatments are 100% effective and few controls – even placebo or no treatment – are without some effect, NNTs for very effective treatments are usually in the range of 2 to 4. An exception to this might be the use of antibiotics. The NNT for *H pylori* eradication with triple or dual therapy, for instance, is 1.1. NNTs may also be calculated for different outcomes; so, to use the same example, the NNT for preventing one ulcer recurrence at one year is 1.8 (Table 2).[1,2]

Larger NNTs can be found with useful interventions – for instance prophylactic measures – where few patients are affected in large populations. Aspirin, which prevents one death at five weeks after a myocardial infarction, has an NNT of 40 but is regarded as beneficial. The same is true for instituting thrombolytic therapy as early as possible

Box 1. The key formula

Calculating a number needed to treat (NNT)

$$\text{NNT} = \frac{1}{(\text{IMPact}/\text{TOTact}) - (\text{IMPcon}/\text{TOTcon})}$$

where:

IMPact = number of patients given active treatment achieving the target

TOTact = total number of patients given the active treatment

IMPcon = number of patients given a control treatment achieving the target

TOTcon = total number of patients given the control treatment

Table 2. Examples of NNTs calculated from systematic reviews[1,2]

	Treatment	Comparator	Duration of intervention	Outcome	NNT (CI)
Peptic ulcer	Triple therapy	Histamine antagonist	6–10 weeks	*Helicobacter pylori* eradication	1.1 (1.08–1.15)
Peptic ulcer	Triple therapy	Histamine antagonist	6–10 weeks	Ulcers remaining cured at 1 year	1.8 (1.6–2.1)
Migraine	Oral sumatriptan	Placebo	Single dose	Headache relieved at 2 hours	2.6 (2.3–3.2)
Postoperative pain	Paracetamol	Placebo	1,000 mg single dose	At least 50% pain relief	3.6 (3.0 to 4.4)
Fungal nail infection	Terbinafine	Griseofulvin	12 or 24 weeks	Cured at 48 weeks	2.7 (1.9–4.5)
Painful diabetic neuropathy	Antidepressant	Placebo		At least 50% pain relief	2.9 (2.4–4.0)
Postoperative vomiting	Droperidol	Placebo	Single dose	Prevention for 48 hours in children undergoing squint correction	4.4 (3.1–7.1)
Peptic ulcer	Triple therapy	Histamine antagonist	6–10 weeks	Ulcers healed at 6–10 weeks	4.9 (4.0–6.4)
Venous thromboembolism	Graduated compression stockings	No stockings		Episodes of venous thromboembolism	9 (7–13)
Anticipated preterm delivery	Corticosteroids	No treatment	Before delivery	Risk of foetal RDS	11 (8–16)
Dog bites	Antibiotics	Placebo	Single course	Infection	16 (9–92)
Hypertension in the elderly	Drug treatments	No treatment	At least 1 year	Overall prevention of cardiovascular event over 5 years	18 (14–25)
Myocardial infarction	Aspirin alone	No treatment		Prevention of one 5-week vascular death	40
Myocardial infarction	Thrombolytic therapy 5 hours earlier	Later treatment		Prevention of one 5-week vascular death	100

CI: confidence interval; NNT: number needed to treat; RDS: respiratory distress syndrome

(beginning thrombolytic therapy five hours earlier has an NNT of 100).[2]

The **'NNT method'** is now also being used in other ways. For example, it **can be used to examine adverse effects of treatments or interventions,** when it becomes the **NNH.** There are few examples, but, for instance, the use of epidural analgesia during childbirth is reported to produce higher rates of caesarean section. If that were regarded as harm, then the NNH would be 10.[1]

Examples of NNT calculations

'The NNT is the reciprocal of the change in absolute risk brought about by an intervention.'

What does this mean? A few examples will serve to show how it works. As always, it is

easier to look at some real examples rather than at meaningless hypothetical calculations, and what follows is a series of examples taken from relatively recent systematic reviews or clinical trials. These are expanded in Table 2 with a series of other examples from the literature.

Example 1. Paracetamol in acute postoperative pain

If you were responsible for organising pain relief after day-case or minor surgery, you would want to make sure that patients had good pain relief. Your first choice of analgesic might well be paracetamol, but then you'd ask yourself – just how good is it as an analgesic in this circumstance? Fortunately, a Cochrane review provides lots of data to help you make your decision.[3]

In 28 randomised trials with 3,200 patients, the results were as follows.

- With paracetamol 975 or 1,000 mg, 876/1,903 (46%) patients with moderate or severe postoperative pain had the outcome of at least 50% pain relief over six hours.
- With placebo, 241/1,329 (18%) patients had the same outcome.

The NNT was, therefore:

1/(876/1,903) – (241/1,329)
= 1/(0.46 – 0.18)
= 1/0.28
= 3.6

For every four patients with moderate or severe postoperative pain, one would have at least 50% pain relief who would not have that relief with placebo. Taking into account that half of those given paracetamol 1,000 mg needed more analgesic within six hours and that, on average, the time to remedication was less than four hours, you might wonder whether there were any alternatives. Fortunately, Cochrane offers lots of evidence on this point (www.cochrane.org/reviews/clibintro.htm).

Example 2. Anti-epileptics in the management of frequent migraine attacks

When people have frequent migraine attacks, a number of measures can be tried to reduce the rate. One measure is the use of anti-epileptic drugs. A Cochrane review reported on randomised, mainly double-blind, trials usually lasting several months.[4] One outcome was the number of patients having at least a 50% reduction in the number of migraine attacks over 28 days, reported in five trials for various forms of valproate.

The review of these trials showed the following results.

- With valproate, 174/383 (45%) patients had the number of migraine attacks reduced by at least half.
- With placebo, 54/259 (21%) had the same outcome.

The NNT was, therefore:

1/(174/383) – (54/259)
= 1/(0.45 – 0.21)
= 1/0.24
= 4.1

So, for every four people with frequent migraine attacks (typically more than two attacks per month), one would have the frequency reduced by half with valproate who would not have achieved this response with placebo.

Example 3. Clopidogrel plus aspirin to prevent vascular events, compared with antiplatelet monotherapy

In certain circumstances, when patients are at a high risk of adverse vascular events, the question is asked whether using two antiplatelet interventions is better than using only one. A systematic review analysed randomised trials comparing clopidogrel plus aspirin with antiplatelet monotherapy.[5] The outcome was any major vascular event, including death, stroke or myocardial infarction. Patients included those with acute coronary syndrome, those undergoing percutaneous coronary intervention and others.

A review of eight randomised trials with over 91,000 patients showed the following results.

- With clopidogrel plus aspirin, 4,883/45,930 (11%) patients had the outcome of death, stroke, or myocardial infarction.

- With monotherapy, 5,790/45,974 (13%) had the same outcome.

The NNT was, therefore:

1/(4,883/45,930) − (5,790/45,974)
= 1/(0.11 − 0.13)
= 1/0.02
= −51

The negative sign here shows that for every 50 people treated with clopidrogel and aspirin rather than antiplatelet monotherapy, one fewer will suffer a major vascular event.

Here the NNT can be given as an NNTp, in which case the sign would alter, and the NNTp would be 51.

Example 4. Statins for people with low cholesterol but elevated C-reactive protein

Media reports suggest that using statins in low-risk men is effective, reducing the risk of heart attack by half. The implication (by the media) is that everyone should be on statins. For further details, please refer to the paper directly.[6]

To be eligible for the study, men had to be at least 50 and women at least 60 years of age. Their LDL-cholesterol levels had to be below 3.4 mmol/l, triglyceride levels had to be below 5.6 mmol/l and C-reactive protein levels had to be 2 mg/l or greater. Although about 18,000 people participated, 90,000 were screened for eligibility. The trial's primary outcome was a complex one of heart attack, stroke, admission for unstable angina, revascularisation and death from cardiovascular cause after five years of treatment with rosuvastatin 20 mg or placebo.

For the trial's primary outcome, the results were as follows.

- With rosuvastatin 20 mg, 142/8,901 (1.6%) participants had the primary outcome.
- With placebo, 251/8,901 (2.8%) had the same outcome.

The NNT was, therefore:

1/(142/8,901) − (251/8,901)
= 1/(0.016 − 0.028)
= 1/−0.012
= −81

For the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes, the results were as follows.

- With rosuvastatin 20 mg, 83/8,901 (0.9%) participants had the combined outcome of myocardial infarction, stroke, or death from cardiovascular causes.
- With placebo, 157/8,901 (1.8%) had the same outcome.

The NNT was, therefore:

1/(83/8,901) − (157/8,901)
= 1/(0.009 − 0.018)
= 1/−0.009
= −120

Again, the negative sign here shows that we are dealing with an NNTp. To prevent one case of myocardial infarction, stroke, or death from cardiovascular causes, we have to treat 120 people with rosuvastatin 20 mg daily for five years.

Example 5. Perioperative beta-blockers in non-cardiac surgery

Should perioperative beta-blockers be used in non-cardiac surgery, or do they cause harm? A useful meta-analysis provides the figures, showing some benefits and some harm.[7] Our main interest is whether there is a problem with perioperative bradycardia requiring treatment, or with perioperative hypotension.

For perioperative bradycardia, the meta-analysis showed the following results.

- With beta-blockers, 308/1,889 (16%) participants had perioperative bradycardia requiring treatment.
- With the control, 120/1,615 (7.4%) had the same outcome.

The NNT was, therefore:

1/(308/1,889) − (120/1,615)
= 1/(0.16 − 0.074)
= 1/0.086
= 12

For perioperative hypotension, the meta-analysis showed the following results.

- With beta-blockers, 460/1,858 (25%)

participants had perioperative hypotension.
- With the control, 280/1,563 (18%) had the same outcome.

The NNT was, therefore:

1/(460/1,858) − (280/1,563)
= 1/(0.25 − 0.18)
= 1/0.07
= 14

Here the NNT becomes the NNH. For every 12 or 14 people treated with beta-blockers perioperatively, there will be one more case of bradycardia and one more case of hypotension.

Implications of NNTs

NNTs are useful in making policy decisions and decisions regarding individual patients. There are some important points to remember, though.

- **NNTs** can be **calculated from any trial data that present dichotomous information.** As in our examples above, information is needed on how many patients achieve a particular treatment benefit, such as pain relief to a certain level, or not dying. So, some thought has to be given to defining a worthwhile outcome.
- When NNTs are calculated, the circumstances are all important. These include the comparison being made (with placebo, or another active treatment), the dose of a drug and/or duration of treatment, and the outcome.
- **Any NNT is just a point estimate.** All point estimates have some uncertainty around them, usually reflected in the 95% CI. For example, an NNT of 5.0 (3.6–7.2) means that 19 times out of 20 the result would fall in the range of 3.6 to 7.2 if the studies were repeated. The CI becomes narrower as the amount of data increases, so large trials give a smaller interval than small trials. NNTs calculated from systematic reviews of randomised controlled trials provide the highest level of evidence.
- **NNTs can be used to calculate different endpoints from the same studies.** Thus the *H pylori* example in Table 2 has three separate endpoints – *H pylori* eradication, ulcer healing at six weeks after treatment and ulcers still cured one year later.
- Comparison across treatments may be sensible, but only when comparisons are on a like-for-like basis. So, comparing NNTs from, say, lipid-lowering in one study with a six-month outcome against another study with a three-year outcome would present some difficulty.
- **NNTs can be used to express other features, such as harm.** Adverse effects of treatment will increasingly be examined in this way and we will begin to see the **NNH** as well as the NNT.
- NNT is only one part of any assessment about purchase of treatment. There are many other factors, including adverse effects, costs, social and medical priorities.
- When clinicians and policy makers were presented with research results in different formats – NNTs, absolute risk reductions (ARRs) and RRRs – they made more conservative decisions when they received treatment effects expressed as NNTs than when they received them as RRRs or ARRs.

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Further reading

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