**The number needed to treat for net effect (NNTnet) as a metric for measuring**

**combined benefits and harms**

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**Abstract**

Calculating the number needed to treat (NNT) has been widely used to help understand treatment effect results of randomized controlled trials (RCTs). Combined benefit-and-harm profiles from RCT results have to be taken into account to maximize benefits and minimize harms. Unfortunately, in the biomedical community there is no easy and acceptable way to incorporate both benefit and harm information of treatments in a single summary statistic similar to an NNT. In this paper, we propose a new metric, the “NNT for net effect” or NNTnet to present the combined benefit-and-harm effects of an intervention or therapy based on NNT-type information with the intention that it will advance decision-making for health professionals, researchers and resource-managers in real-world practice. Examples are provided to illustrate the calculation and application of the NNTnet in practice. An NNTnet is specifically applicable to the physicians and resource-managers who interpret the data published in the literature to help with their decision-making and the researchers who present the trial data to the audiences in their papers and presentations, all of whom used to employ NNT information to show and interpret beneficial and harmful effects separately.

**Keywords:** number needed to treat; benefit; harm; number needed to treat for net effect

**Introduction**

Since its introduction in 1988, the number needed to treat (NNT) has been widely used to help understand treatment effect results of randomized controlled trials (RCTs) [1](#_ENREF_1). The NNT can be further specified as NNT for benefit (NNTB) or NNT for harm (NNTH). The metric of NNT is calculated as the reciprocal of the absolute risk reduction (ARR) or absolute risk increase (ARI), denoting that on average, how many patients are needed to treat with a specific therapy either 1) to achieve one additional benefit outcome or prevent one additional adverse event (NNTB)or 2) to develop a harmful outcome or experience an adverse event (NNTH), as compared to the control experience. The concept of NNT is substantially helpful in clinical decision-making because it is intuitive, simple, straightforward and interpretable to convey the clinical and statistical information to health professionals who may share this information with their patients [2](#_ENREF_2). As well, in clinical practice the NNT can be used to extrapolate results of an RCT to individual patients with different baseline risks assuming the relative risk reduction is constant, further assisting physician-patient shared decision-making [3](#_ENREF_3).

Most treatments not only improve patients’ outcomes but also increase the risks of adverse side effects. The combined benefit-and-harm profiles from RCT results have to be taken into account for all the stakeholders to maximize benefits and minimize harms. Unfortunately, in the health research community there is no easy and acceptable way to incorporate both benefit and harm information of treatments into a single summary statistic similar to an NNT. One of the approaches, referred to as the “likelihood to be helped or harmed (LHH)” is the ratio of 1/NNTB:1/NNTH (aka, the ARR:ARI) [4](#_ENREF_4). LHH is interpreted as the number of times the treatment is likely to help a patient as to harm the patient. This trade-off illustration may incorporate the benefit-and-harm information, patients’ baseline risks, and patient values and preferences to support decision-making [4](#_ENREF_4). However, it is less intuitive for understanding, as it replaces the use of natural units that are incorporated into the NNT, e.g., NNT=20 means treating 20 patients will produce one additional benefit (or harm) event while the treatment will have no effect on the other 19. Instead the LHH produces a unitless metric (ratio) which is open to various inferences and clinical interpretations. Therefore, its acceptability and applicability in clinical practice is limited. By contrast, the “net benefit” approach that by direct definition indicates the beneficial effects deducted by the harmful effects, has been widely used in the literature and may be an attractive measure to help with prompt and straightforward comprehension of the treatment effects on clinical services [5](#_ENREF_5). Nevertheless, no studies have explicitly employed the NNT information embedded in a net benefit (or harm) approach, which leaves an important research gap between the net benefit (or harm) concept and the NNT application.

In this paper, we propose a new metric named “NNT for net effect” (NNTnet) to present the combined benefit-and-harm effects of an intervention or therapy based on NNT-type information with the intention that it will advance decision-making for health professionals, researchers and resource-managers in real-world practice. We also provide examples to illustrate the calculation and application of NNTnet in practice. An NNTnet is specifically applicable to the physicians and resource-managers who interpret the data published in the literature to help with their decision-making and the researchers who present the trial data to the audiences in their papers and presentations, all of whom used to employ NNT information to show and interpret beneficial and harmful effects separately.

**Methods and examples**

First we briefly summarize the related terms and definitions for calculation of NNT in **Box 1**. Imagine we are conducting an RCT to explore whether and to what extend the treatment will reduce the rate of an undesirable event for a fixed time period. Using the event rates in the control group (CER) and the experimental group (EER), we can report the relative risk (RR, calculated as *EER/CER*), relative risk reduction (RRR, calculated as *(CER-EER)/CER*) or *(1-RR))*, and absolute risk reduction (ARR, calculated as *CER-EER*). Note that the ARR can be also calculated as *(Baseline risk) × (1-RR)* or *(Baseline risk) × RRR.* The NNTB is therefore derived from *1/ARR*. The same concept and calculation apply to the NNTH when the treatment causes more of the undesirable events than the control group.

***1. NNTnet calculation***

The absolute risk reduction for net effect (ARRnet) can be defined as the absolute difference between ARR and ARI [6](#_ENREF_6); that is, ARRnet = ARR – ARI (1).

Then we can calculate the NNTnet as the reciprocal of the ARRnet; that is,

NNTnet = 1/ARRnet = 1 / (ARR - ARI) = 1/ (1/NNTB – 1/NNTH) (2)

The clinical interpretation of NNTnet is similar to that of NNT, which is on average, how many patients are needed to treat with a specific therapy to receive one additional net effect on the combined benefit-and-harm outcome over the control group; or in other words, the NNTnet is the average number of patients who are needed to be treated to see the benefit exceeding the harm by one event. Of note, the NNTnet can have a negative result, which can be interpreted similarly as a negative NNT (aka, NNTH). Therefore, a negative NNTnet corresponds to the number of patients who are needed to treat with the therapy, on average, to develop one additional net harmful effect on the combined benefit-and-harm outcome over the control group, or in other words, the average number of patients needed to treat to see the harm exceeding the benefit by one event.

*Hypothetical example 1*

For a simple practice, now we use the NNTnet in a straightforward hypothetical example.

*An antipsychotic treatment for patients with dementia reduces hospitalization for delirium (NNTB = 60) but also increases hospitalization for pneumonia (NNTH = 90).*

We can apply equation (2) to calculate the NNTnet as 180 (that is, 1/(1/60 – 1/90) = 180). Therefore the NNTnet of this treatment indicates that on average for every 180 patients treated, there will be one additional beneficial effect (less hospitalization for delirium) more than a harmful effect (more hospitalization for pneumonia), or in other words, one less hospitalization for whatever reasons.

***2. Baseline risks, relative effects, multiple outcomes, and outcome weighting***

The NNTnet approach can incorporate the information regarding patients’ baseline risks, treatment relative effects, multiple outcomes, and the weighting for outcomes. If possible, we may compare our patient’s characteristics with those from RCT patients, especially from the relevant subgroup of patients, and decide the similarity of baseline risk for our patients. However, it is difficult to capture and use such subgroup data from published trials in the real word. We can also use clinical judgment or validated prediction rules to estimate our patient’s individual baseline risk relative to the risks for the RCT patients. Accordingly, we can calculate the ARR and ARI by taking *(Baseline risk) × (1-RR)* and *(Baseline risk) × |1-RR|* respectively, which can then estimate the NNTnet using equation (2). Similarly, if the evidence of the treatment relative effects (i.e., RR) for different subgroups is available, we can use that information to calculate the different NNTnet for the subgroups. Nevertheless, it is not uncommon to assume the RR is constant across different subgroups for the NNT calculations, especially when no evidence of the RR on risk stratification is available[3](#_ENREF_3).

When there are multiple outcomes of concern, we can use different ARRs and ARIs corresponding to different outcomes for the NNTnet calculations. Therefore the equation (2) can be modified as:

NNTnet = 1/ARRnet = 1 / (∑ARRi - ∑ARIj) = 1/ (∑(1/NNTBi) –∑(1/NNTHj)) (3)

One particular issue may be the choices of outcomes. In general, an NNTnet should be used for the most clinically relevant outcomes that are directly related to treatment consequences of concern. Such outcomes should be reported in a trial with specific emphases from a clinical point. For example, the primary beneficial and harmful outcomes should be included in the NNTnet; the moderately harmful outcomes that frequently occur during the trial implementation, and the severely harmful outcomes that even occur rarely but are of specific concern, can also be considered in the NNTnet; some surrogate outcomes (‘soft outcomes’) that are not significantly clinically relevant, should not be selected for NNTnet calculation. Taken together, the key principle in choosing outcomes is the clinical judgement from the NNTnet-users, which forms the solid base to advance their understanding, interpretations and decision-making while reading the trial data from the literature.

However, the outcomes may not be of equal importance, which therefore requires different weighting for the individual outcomes. We recommend using the weighting for the primary benefit outcome of 1 to reflect the most important finding in a trial, while all other outcomes’ weighting represents the importance relative to the primary benefit outcome. The weighting values should be, ideally, from the validated utility scoring system published in the literature. However, such a scoring system may not always be available. In that case, the NNTnet-users may either elicit their own weighting to reflect their interpretations and clinical judgement on the different outcomes, or choose to treat all the outcomes as of equal importance and acknowledge the related limitations. When weighting is used, consequently the equation (3) is further developed as:

NNTnet = 1/ARRnet = 1 / (∑wti*×*ARRi - ∑wtj*×*ARIj) = 1/ (∑wti*×*(1/NNTBi) –∑wtj×(1/NNTHj)); where wt = weighting (4)

Unlike the general weighting practice, we do not require the sum of weighting to be 1. This is an advantage as it would allow more flexibility of weighting for adding or excluding outcomes in different scenarios and settings. Also, while the weighting aims to reflect an importance of different outcomes relative to the primary benefit outcome, calculating the sum of weighting is less clinically relevant or necessary.

Of note, the NNTnet calculated based on the information tailored on a certain patient’s individual characteristics (such as baseline risk, relative effect, multiple outcomes, and outcome weighting) can be interpreted as how many patients with similar characteristics to *that* patient, on average, are needed to treat to obtain one additional net effect on the combined benefit-and-harm outcome. Nevertheless, it is not quite realistic to calculate NNTnet using an individual patient’s information in a busy clinical service. Therefore we must acknowledge that, similar to an NNT, the NNTnet should always be used based on population-level data from the published trial data, and such NNTnet is always pragmatically used to generalize to all the patients. Thus, again, an NNTnet is especially helpful for physicians, resource-mangers and researchers who interpret the published trial data and make their decisions on a population-based level.

*Hypothetical example 2*

An oral anti-diabetic agent is used to treat patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). It is reported that the agent can reduce risks of all-cause death and end stage renal disease (ESRD); however, it can also increase risks of myocardial infarction (MI) and hospitalization due to severe infection. Some hypothetical statistics are displayed in **Table 1**.

**Table 1.** Benefit-and-harm outcomes for the anti-diabetic agent used to treat patients with T2DM and CKD

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Baseline risk** | **RR** | **ARR or ARI** | **NNTB or NNTH** | **Weighting**  |
| *Benefit outcomes* |
| All-cause death (high risk)1 | 10/1000 | 0.5 | 0.005 | 200 | 1.0 |
| All-cause death (low risk)2 | 5/1000 | 0.5 | 0.0025 | 400 |
| ESRD | 3/1000 | 0.4 | 0.0018 | 556 | 0.6 |
| *Harm outcomes* |
| MI (high risk)3 | 2/1000 | 2.5 | 0.003 | 334 | 0.8 |
| MI (low risk)4 | 1/1000 | 2.0 | 0.001 | 1000 |
| Hospitalization due to severe infection | 2/1000 | 1.5 | 0.001 | 1000 | 0.2 |

1Categorized as high risk in the subgroup of patients with age > 70 years;

2Categorized as low risk in the subgroup of patients with age < 70 years;

3Categorized as high risk in the subgroup of patients with heart failure;

4Categorized as low risk in the subgroup of patients without heart failure

In this hypothetical example, there are multiple outcomes (2 benefit and 2 harm outcomes) of interest. Patients can have different baseline risks (such as death risk stratified by age, and MI risk stratified by with or without heart failure), different treatment relative effects for different outcomes (such as larger RR for death than for ESRD, and larger RR for MI than for hospitalization), different treatment relative effects for the same outcome (such as larger RR for MI in high-risk subgroup than in low-risk subgroup), and different weighting for different outcomes. Therefore, for instance, regarding the patients aged > 70 years (high risk of death) and with heart failure (high risk of MI):

*A.* if we only consider death and MI, the NNTnet will be 500 (i.e., 1/(0.005-0.003)); this denotes that 500 patients with similar characteristics, on average, are needed to be treated with the anti-diabetic agent to experience the benefit (less all-cause death) exceeding the harm (more MI) by one event.

*B.* if we consider all the four outcomes, the NNTnet will be 358 (i.e., 1/(0.005 + 0.0018 - 0.003 - 0.001); it indicates that on average 358 patients are needed to be treated to see the benefit (less all-cause death and less ESRD) exceeding the harm (more MI and more hospitalization) by one event. Because the ARR for ESRD (0.0018) is larger than the ARI for hospitalization (0.001) yielding to an increased ARRnet, the NNTnet (358) becomes smaller than in the scenario *A* above (500) accordingly.

*C.* if we consider the weighting for all the four outcomes, the NNTnet will be 288 (i.e., 1/(1.0×0.005 + 0.6×0.0018 - 0.8×0.003 - 0.2×0.001)). Likewise, the NNTnet denotes that on average, 288 patients are needed to be treated to obtain the benefit (more MI and more hospitalization) exceeding the harm (more MI and more hospitalization) effect by one event, after taking different weighting of the outcomes into account. The NNTnet is smaller than in the scenario *B* (358), reflecting the impact of different weighting for various outcomes on the NNTnet results.

***3. Graph of NNTnet and confidence interval***

As shown in the equations (2) to (4), the NNTnet follows a simple reciprocal function of the ARRnet, which results in two asymptotic lines, one in the first and one in the third quadrant (**Figure 1**). The graph in the first quadrant applies to the positive NNTnet for a net beneficial effect, while the graph in the third quadrant is for the negative NNTnet for a net harmful effect. The ARRnet ranges from -1 to +1, which therefore leads to the NNTnet ranging from +1 to +∞ and from -∞ to -1. An NNTnet closer to 1 indicates a stronger clinical impact, because it implies that fewer patients are required to receive the treatment to experience one net effect on the combined benefit-and-harm outcome. Therefore, with a positive NNTnet the lower the number the better while for a negative NNTnet the lower the number the worse are the consequences, although any NNTnet represented by a negative value reflects an undesirable net effect.

We can take the reciprocal of the ARRnet confidence interval to calculate the confidence interval of an NNTnet. The confidence interval of the ARRnet can be calculated as ARRnet ± 1.96 SE(ARRnet), where SE(ARRnet) is the standard error. One of the most commonly-used methods to calculate the SE(ARRnet) is to employ the SE(ARR) and SE(ARI) by using the formula of $\sqrt{SE(ARR)^{2}+SE(ARI)^{2}}$. However this approach does assume that benefit outcomes and the harm outcomes are independent of each other. Nevertheless, alternatively if the information on the correlation between ARR and ARI is available, the variance of the ARRnet can be updated as V(ARR) + V(ARI) + 2\*COV(ARR, ARI), or V(ARR) + V(ARI) + 2\*r\* V(ARR)\*V(ARI), where V is variance, COV is covariance, and r is the correlation between ARR and ARI. When the SEs of ARR and ARI are not reported, it is straightforward and simple to calculate the SEs based on the contingency tables, if the trial reports a binary outcome. If the outcome is survival time of event, we would refer readers to the guidance paper for calculation of the SEs of ARR and ARI [7](#_ENREF_7). Nevertheless, it is challenging to show the confidence interval of NNTnet when the ARRnet is not statistically significant, because the NNTnet confidence interval will include infinity. Again, we would refer readers to another paper showing how to report the NNT (and NNTnet) confidence interval when the ARR (and ARRnet) is not statistically significant [8](#_ENREF_8).

**Example based on data reported from a published RCT, ENGAGE-AF-TIMI 48**

The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial was conducted to explore the efficacy and safety of edoxaban in a median of 2.8 years as compared with warfarin in patients with atrial fibrillation for stroke prevention [9](#_ENREF_9). The high dose of edoxaban (60 mg once-daily) was found to be associated with lower risk of stroke or systemic embolism (benefit outcome); however as an oral anticoagulant, it may also cause more bleeding events (harm outcome). For the purpose of illustration, we only chose the data of one benefit outcome (stroke or systemic embolism) and two harm outcomes (intracranial bleeding and major gastrointestinal bleeding) (**Table 2**). The weighting of the outcomes was determined from a published study, where it assigned one-point to stroke or systemic embolism and 1.5-point to intracranial bleeding [10](#_ENREF_10). We allocated an arbitrary weighting of 0.5-point to gastrointestinal bleeding, for the completion of this practice.

If no weighting is considered, the ARRnet is 0.005 (95% confidence interval: -0.004 to 0.014). Thus the NNTnet is 200 (95% confidence interval: NNTH 250 to  to NNTB 72) as calculated by using equation (3). Taking the weighting into calculation yields the ARRnet of 0.0087 (95% confidence interval: 0.001 to 0.017), which produces the NNTnet of 115 (95% confidence interval: NNTB 59 to 1000) according to equation (4). The interpretation of the latter NNTnet is that, on average we need to treat 115 patients with atrial fibrillation with the high-dose edoxaban to achieve one additional net beneficial effect on the combined benefit-and-harm outcome. Given its impressive treatment effect relative to warfarin, edoxaban was approved by the US FDA (food and drug administration) in 2015 [11](#_ENREF_11), and now has been recommended in guidelines of atrial fibrillation management [12-15](#_ENREF_12).

**Table 2**. Edoxaban versus warfarin in patients with atrial fibrillation for stroke prevention in a median of 2.8 years (data from ENGAGE AF-TIMI 48)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Outcome** | **Baseline risk** | **RR** | **ARR or ARI** | **NNTB or NNTH** | **Weighting**  |
| *Benefit outcome* |
| Stroke or systemic embolism prevention | 1.50%  | 0.79 | 0.00321 | 313 | 1.0 |
| *Harm outcome* |
| Intracranial bleeding  | 0.85% | 0.46 | -0.00462 | -218 | 1.5 |
| Major gastrointestinal bleeding | 1.23% | 1.23 | 0.00283 | 358 | 0.5 |

1 The SE for ARR was 0.003 as calculated from the published data;

2 The SE for ARI was 0.001;

3 The SE for ARI was 0.003

**Discussion**

Given its simplicity, convenience and interpretability, the NNT has been widely used in the RCT literature to inform recommendations and decision-making for health professionals [16](#_ENREF_16),[17](#_ENREF_17). The NNTnet approach that we demonstrate here is a new metric to combine benefit and harm profiles by using the NNT concept into a single value, delivering the efficacy and safety information of a treatment simultaneously to advance decision-making in real-world settings. The NNTnet may own a unique clinical acceptability by combining the benefit-and-harm information quantitatively from published RCTs, especially when compared with the NNTB and NNTH that are presented separately in the trial literature. Of importance is that when NNTB and NNTH are presented separately they cannot be combined algebraically by the clinicians and must be addressed separately in the decision-making process. The NNTnet calculation is flexible and straightforward, and theoretically, can take into account patients’ baseline risks, multiple outcomes, outcome weighting, and different relative treatment effects.

Of note, there is no strict requirement on the benefit-and-harm effect for the application of NNTnet, which denotes that the NNTnet can be widely and flexibly employed with the use of the published trial data especially the contingency tables. After calculating an NNTnet by incorporating the benefit and harm effect, physicians, resource-managers and researchers can have a prompt and straightforward sense of how many patients on average needed to be treated to see the benefit exceeding the harm effect by one event. This metric can also be expected to assist with physician-patient decision-making in clinical practice.

Nevertheless, the ARRnet is calculated strictly based on the additive algorithm from ARR and ARI, thereby limiting the application of ARRnet (and NNTnet) when a jointly and overlapped relationship between ARR and ARI becomes an issue of concern, even though it is not commonly encountered in busy clinical practice in the real world. Lack of simplicity when taking multiple outcomes, different weighting and treatment effects into account also compromises the prompt reproductivity of NNTnet in communication with the audiences. Furthermore, similar to the NNT’s limitation, the NNTnet is less informative to intrapolate or extrapolate the estimations in a different time period or in a different comparison pair [3](#_ENREF_3). For instance, the NNTnet in a median of 2.8-year follow-up in the ENGAGE AF-TIMI 48 cannot be used to accurately estimate an NNTnet in 5- or 10-year follow-up, because the NNTnet calculation is usually time-dependent on the fixed time frame in the published RCT. Even though the RR can be assumed to be constant and the baseline risk can be estimated from survival curves, the extrapolation of an NNTnet for a longer follow-up is less direct and fraught with potential errors [16](#_ENREF_16). Likewise, the NNTnet for edoxaban versus warfarin cannot be used to infer an NNTnet for edoxaban versus aspirin. Besides, the choice of outcomes and the outcome weighting may allow arbitrary input from different NNTnet-users. This is inevitable because it reflects the individualized clinical judgement from different knowledge-consumers including physicians, resource-mangers, and researchers. Similar to an NNT that is calculated based on population-level data, the NNTnet is generally used for population-based judgement. Theoretically, the NNTnet can incorporate individual patient’s characteristics including his/her own baseline risks, choices of outcomes, outcome weighting, and relative treatment effects; this practice is not feasible or realistic due to either no such data available or a busy clinical schedule.

To summarize, we have presented a new metric to combine the benefit and harm information of a treatment using the widely-accepted NNT approach. Should the NNTnet metric be further tested and validated, it has the potential to facilitate the knowledge intake from the published RCTs and enhance decision-making for health professionals, researchers and resource-managers in real-world practice.

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**Box 1.** Some NNT-related terms and their definitions

|  |
| --- |
| When the treatment is expected to reduce the probability of an adverse event for a fixed time period:  |
| **Event rate (ER)**: the number of participant experiencing an outcome of interest; can be separated into **control event rate (CER)** in the control group and **experimental event rate (EER)** in the intervention group |
|  |
| **Relative risk (RR)**: the ratio of the event rate in the intervention group to the event rate in the control group, calculated as *EER/CER* |
|  |
| **Relative risk reduction (RRR)**: the difference in event rates between the control and intervention groups, calculated as the proportion of reduced event rate in the control group *(CER-EER)/CER* or *(1-RR)* |
| **Relative risk increase (RRI):** the difference in event rates between the two groups, used when there are more adverse events in the intervention group than in the control group, calculated as *|CER-EER|/CER* or *|1-RR|* |
| **Absolute risk reduction (ARR)**: the absolute arithmetic difference in event rates between the two groups, calculated as *CER-EER*, or *(Baseline risk) × (1-RR),* or *(Baseline risk) × RRR*  |
|  |
| **Absolute risk increase (ARI)**: the absolute arithmetic difference in event rates, used when there are more adverse events in the intervention group than in the control group, calculated as |*CER-EER|*, or *(Baseline risk) × |1-RR|, or (Baseline risk) × RRI* |
|  |
| **NNT for benefit (NNTB):** the number of participants needed to be treated to prevent one additional adverse event, calculated as *1/ARR* |
|  |
| **NNT for harm (NNTH):** the number of participants needed to be treated to develop one additional adverse (or harmful) event, calculated as *1/ARI* |

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**Figure 1.** Graph of the NNTnet and ARRnet

Please see attached the figure