

Are the results of the trial valid? (Internal Validity)

What question did the study ask?

- Patients
- Intervention
- Comparison
- Outcomes

1a. R- Was the assignment of patients to treatments randomised?

What is best?

Centralised computer randomisation is ideal and often used in multi-centred trials. Smaller trials may use an independent person (eg the hospital pharmacy) to 'police' the randomization.

Where do I find the information?

The Methods should tell you how patients were allocated to groups and whether or not randomisation was concealed.

In this paper

Yes

No

Unclear

Comment:

1b. R- Were the groups similar at the start of the trial?

What is best?

If the randomisation process worked (that is, achieved comparable groups) the groups should be similar. The more similar the groups the better it is. There should be some indication of whether differences between groups are statistically significant (ie. p values).

Where do I find the information?

The Results should have a table of 'Baseline Characteristics' comparing the randomized groups on a number of variables that could affect the outcome (ie age, risk factors etc). If not, there may be a description of group similarity in the first paragraphs of the Results section.

In this paper

Yes

No

Unclear

Comment:

2a. A – Aside from the allocated treatment, were groups treated equally?

What is best?

Apart from the intervention the patients in the different groups should be treated the same, eg additional treatments or tests.

Where do I find the information?

Look in the Methods section for the follow-up schedule and permitted additional treatments etc, and in Results for actual use.

In this paper

Yes

No

Unclear

Comment:

2b. A – Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?

What is best?

Losses to follow-up should be minimal – preferably less than 20%. However, if few patients have the outcome of interest, then even small losses to follow-up can bias the results. Patients should also be analysed in the groups to which they were randomised – ‘intention-to-treat analysis’.

Where do I find the information?

The Results section should say how many patients were randomised (eg Baseline Characteristics table) and how many patients were actually included in the analysis. You will need to read the results section to clarify the number and reason for losses to follow-up.

In this paper

Yes

No

Unclear

Comment:

3. M – Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

What is best?

It is ideal if the study is ‘double-blinded’ – that is, both patients and investigators are unaware of treatment allocation. If the outcome is objective (eg death) then blinding is less critical. If the outcome is subjective (eg symptoms or function) then blinding of the outcome assessor is critical.

Where do I find the information?

First, look in the Methods section to see if there is some mention of masking of treatments eg placebos with the same appearance or sham therapy. Second, the Methods section should describe how the outcome was assessed and whether the assessor(s) were aware of the patients’ treatment.

In this paper

Yes

No

Unclear

Comment:

What were the results?

1. How large was the treatment effect?

Most often results are presented as dichotomous outcomes (yes or no outcomes that happen or don't happen) and can include such outcomes as cancer recurrence, myocardial infarction and death. Consider a study in which 15% (0.15) of the control group died and 10% (0.10) of the treatment group died after 2 years of treatment. The results can be expressed in many ways as shown below.

What is the measure?

Relative Risk (RR) = risk of the outcome in the treatment group / risk of the outcome in the control group.

In our example the $RR = 0.10/0.15 = 0.67$

Absolute Risk Reduction (ARR) = risk of the outcome in the control group - risk of the outcome in the treatment group. This is also known as the absolute risk difference.

In our example the $ARR = 0.15 - 0.10 = 0.05$ or 5%

What does it mean?

The relative risk tells us how many times more likely it is that an event will occur in the treatment group relative to the control group. An RR of 1 means that there is no difference between the two groups thus, the treatment had no effect. An $RR < 1$ means that the treatment decreases the risk of the outcome. An $RR > 1$ means that the treatment increased the risk of the outcome.

Since the $RR < 1$, the treatment decreases the risk of death.

The absolute risk reduction tells us the absolute difference in the rates of events between the two groups and gives an indication of the baseline risk and treatment effect. An ARR of 0 means that there is no difference between the two groups - therefore the treatment had no effect.

The absolute benefit of treatment is a 5% reduction in the death rate.

Relative Risk Reduction (RRR) = absolute risk reduction / risk of the outcome in the control group. An alternative way to calculate the RRR is to subtract the RR from 1 (eg. $RRR = 1 - RR$)

In our example the $RRR = 0.05/0.15 = 0.33$ or 33%

Or

$RRR = 1 - 0.67 = 0.33$ or 33%

Number Needed to Treat (NNT) = inverse of the ARR and is calculated as $1 / ARR$.

In our example the $NNT = 1 / 0.05 = 20$

The relative risk reduction is the complement of the RR and is probably the most commonly reported measure of treatment effects. It tells us the reduction in the rate of the outcome in the treatment group relative to that in the control group.

The treatment reduced the risk of death by 33% relative to that occurring in the control group.

The number needed to treat represents the number of patients we need to treat with the experimental therapy in order to prevent 1 bad outcome and incorporates the duration of treatment. Clinical significance can be determined to some extent by looking at the NNTs, but also by weighing the NNTs against any harms or adverse effects (NNHs) of therapy.

We would need to treat 20 people for 2 years in order to prevent 1 death.

2. How precise was the estimate of the treatment effect?

The true risk of the outcome in the population is not known and the best we can do is estimate the true risk based on the sample of patients in the trial. This estimate is called the point estimate. We can gauge how close this estimate is to the true value by looking at the confidence intervals (CI) for each estimate. If the confidence interval is fairly narrow then we can be confident that our point estimate is a precise reflection of the population value. The confidence interval also provides us with information about the statistical significance of the result. If the value corresponding to no effect falls outside the 95% confidence interval then the result is statistically significant at the 0.05 level. If the confidence interval includes the value corresponding to no effect then the results are not statistically significant.

Will the results help me in caring for my patient? (External Validity/Applicability)

The questions that you should ask before you decide to apply the results of the study to your patient are:

- Is my patient so different to those in the study that the results cannot apply?
- Is the treatment feasible in my setting?
- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?

THERAPY STUDY

