

Journal club 101 for the new practitioner: Evaluation of a clinical trial

With a large amount of medical information emerging daily, it is impossible for any practitioner to read every medical publication. For example, 6 million new medical articles are published each year; reading 2 articles per day for a year would leave you 82 centuries behind at the end of one year.^{1,2} As new practitioners, we must learn to evaluate the literature in a timely and efficient manner. This article suggests ways to aid new pharmacists in the evaluation of a clinical trial.

Determining relevance.²⁻⁵ First, it must be determined if a published clinical trial is worth reading. Read the title and the abstract and ask the following questions:

1. Did the authors study a clinically important and relevant outcome? For example, a study on whether a therapy decreases morbidity and mortality is more useful than a study on whether the therapy improves a laboratory value or surrogate marker.
2. Is the problem addressed in the trial relevant to your practice?
3. Will this information, if true, require you to change your current practice?

Determining validity.²⁻⁵ The evaluation of a trial's validity takes into account the population studied, the study design, and how the study was conducted. Ask yourself the following questions when reading the methods section of a clinical trial:

1. Are the patients studied similar enough to your patients that you can apply the

- results in your practice?
2. Was it a controlled trial?
3. Were the subjects randomly assigned to the treatment and control groups?
4. Were steps taken to conceal the treatment assignment from study personnel who enrolled and allocated patients in the study? This is not the same as blinding a clinical trial. Allocation refers to the potential for an investigator to know to which group the subjects will be assigned before they enter the study. For example, a clinician may be more likely to enter a patient into the trial if he or she knows that the patient will be allocated to the treatment group. This information can affect which patients are enrolled in a trial and bias the results.
5. Were patients and study personnel blinded to treatment? In other words, did the patients or the treating physicians know to which group each patient was assigned? When the patients and the treating physicians are blinded, the trial is double blind. In triple-blind trials, patients, treating physicians, and investigators assessing the outcomes are all unaware to which group each patient has been assigned. Blinding helps ensure that differences in the treatment group and the control group are due to the effect of therapy rather than the pla-

cebo effect (i.e., expectations that a physician, patient, or investigator may have regarding the therapy being studied).

6. Were all patients who entered the trial properly accounted for at its conclusion, including those who dropped out of the trial? If the authors of the trial do not provide a diagram, it may be helpful to draw a simple flow chart to make sure that all patients have been accounted for. This practice can make it easier to determine how many patients dropped out of the trial or were lost to follow-up and when. It also helps determine the number of patients included and analyzed in the results. You should also read the methods section carefully to determine if follow-up was complete and all patients were included in the analysis of results (i.e., "intention-to-treat" analysis). In this type of analysis, all patients in each group are taken into account in the analysis and comparison of outcomes, including those who did not receive treatment or dropped out of the study. This approach attempts to mimic realistic clinical situations in which not all patients are compliant to treatment. In other words, if a therapy is used in clinical practice, some patients may receive it incorrectly or not receive it at all. There may also be other changes in a patient's care that affect the therapy used. Thus, if a therapy is beneficial after the intention-to-treat

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analysis, despite noncompliance and dropouts, it is more likely that the therapy will be beneficial in actual practice.

7. Were the treatment and control groups similar? This information can usually be found in the first table of most published clinical trials. This table usually gives information about patient demographics and other baseline characteristics of both treatment and control groups. Randomization can reduce the likelihood of imbalances in patient characteristics between groups, especially if treatment is allocated. However, significant differences can still occur between groups and may affect the results of a trial. The difference in outcomes between the groups may not be due to the effect of the treatment but due to inherent differences between the groups. Thus, the more similar the intervention and treatment groups, the more likely it is that any differences seen as a result of the intervention are actually due to the therapy itself, rather than extemporaneous factors.

Evaluating the results.^{2,4} Finally, you must evaluate the results to determine if and how they will change your current treatment strategies.

What were the results? Make a list of the efficacy endpoints of the trial. List the percentage of patients with a particular outcome in the treatment group and the percentage of those in the control group. Use the percentages to calculate the relative risk reduction (RRR) and absolute risk reduction (ARR).^{2,4} The ARR is the difference in the event rate between the control and treatment groups. The RRR estimates the comparative risk reduction between patients given a certain treatment and those not given the therapy. ARR and RRR both describe the efficacy of a treatment but in different ways.

$$\text{ARR} = \text{event rate in the control group} - \text{event rate in the treatment group}$$

$$\text{RRR} = \text{ARR}/\text{event rate in the control group}$$

The ARR indicates the actual difference in outcome between the two groups. For example, if 20% of people died in the control group and 15% of people died in the treatment group, the ARR for death was 5%. The RRR indicates the difference in outcome between the groups while taking into account the frequency of the event in a controlled population. For example, if 20% of the control group and 15% of the treatment group died, the RRR for death was 25% with the treatment. If the rate of death was 100% in the control group and 75% in the treatment group, this would result in a larger ARR (25%), but the RRR would still be 25%.

The rate of adverse effects can be compared using similar concepts. For each adverse effect, list the percentage of patients experiencing that effect in the treatment group and the percentage of those in the control group. Calculate the ARR to determine the increase in each adverse effect associated with the therapy.

$ARR = \text{adverse effect rate in the treatment group} - \text{adverse effect rate in the control group}$

For example, if vomiting occurs in 80% of the treatment population and 60% of the control group, then the absolute risk of the adverse reaction, vomiting, is 20%. The relative risk of adverse effects can be calculated in an equation similar to RRR.

Are the results clinically and statistically significant? Statistical significance explains how likely it is that a difference seen between the treatment and the control groups could have occurred by chance.

Many authors provide the confidence interval for each endpoint. The confidence interval is a measure of the variability or estimate of error in the data. A 95% confidence interval, which is commonly used in clinical trials, is a range of values that contains the true value for the population 95% of the time. If the confidence interval of the ARR includes 0 or the confidence interval of the RRR includes 1, the difference between the treatment and control groups is not significant.

Another indicator of significance is the p value. If the p value is less than or equal to α , (i.e., the probability of a Type I error), the difference is significant. If the p value is greater than α , the difference is not significant. Alpha is usually set at 0.05 unless otherwise indicated. A p value of 0.05 means that the probability of the difference between the two groups being due to chance is 5%.

Clinical significance is more difficult to determine and often based on clinical judgment. The number needed to treat (NNT) can be calculated to help determine the impact of the treatment. The NNT is the number of patients needed to receive a treatment for one patient to benefit from a treatment. The lower the NNT, the larger the impact of the inter-

vention. For each endpoint, calculate the NNT using the following equation:

$$NNT = 1/ARR$$

The number needed to harm (NNH) can be calculated for adverse effects. The NNH is the number of patients needed to receive the treatment for one adverse event to occur. The larger the NNH, the lower the risk of encountering the adverse effect. The NNH can be calculated using the same equation used to calculate the NNT.

Did the study have adequate statistical power? The power of a study is the ability of the study design to detect a statistical difference between groups. Power is dependent on sample size. If the trial shows that there was not a benefit of the treatment studied, power will indicate if there were enough people in the study to detect a difference. In a trial with poor power, there may actually be a benefit that was not detected because the treatment was not studied in enough patients. In most cases, power is calculated before implementing a trial. The calculation is based on an estimation of the number of participants needed to discover a difference between an intervention and control. It takes into account factors such as the incidence of the studied outcome in a control population as well as other considerations. For example, if 1 death occurs in 100,000 patients in a population similar to the patients being studied, many more people would need to be enrolled to ensure the study has adequate power than if the incidence of death is 1 in 10 in the population. There are also other factors, such as lower-than-expected patient recruitment rates or fewer-than-anticipated occurrences of the studied events in the control population. Based on the estimated magnitude of the impact of these factors on the results of the trial, the authors may or may not choose

to recalculate the power of their study when analyzing the results.

What other factors should be considered when evaluating a study? It is also important to consider the strengths and the limitations of each clinical trial. These strengths and weaknesses can be anything from differences in group demographics and drop-out rates to poor reporting of results. Outline all the possible strengths and weaknesses of the clinical trial you evaluate.

How will the study change your practice? Will it affect all of your patients or just some? Do you need to change protocols or clinical pathways based on the results?

Conclusion. These basic steps will assist in selecting clinical trials that are relevant to your practice. As new practitioners, becoming comfortable with evaluating clinical trials is key in remaining up-to-date on the most current therapies that will affect the morbidity, mortality, quality of life, and well-being of your patients.

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