

- Medicine, How to Practice and Teach EBM. 2nd Edition, Churchill Livingstone 2000.
- Hennekens C, Buring J. (1987) Chapter 6 "Case-control studies" in Hennekens CH, Buring JE, Mayrent SL (eds) Epidemiology in Medicine Boston, Little Brown.
  - Rothman KJ, Greenland S. (1986) "Case-control studies". Chapter 7 in Modern Epidemiology 1st edition Rothman KJ (ed), Boston, Little Brown.
  - Rothman KJ, (1986) Cohort Studies. Chapter 6 in Modern Epidemiology, 1st Edition, Boston, Little Brown; Rothman KJ, Greenland S.
  - Breslow NE, Day NE. (1987) Volume 2. "The design and analysis of cohort studies" Chapter 1 in Breslow NE, Day NE, Gart JJ, et al (eds) Statistical methods in cancer research Lyon International Agency for research on Cancer.
  - Hennekens CH, Buring JE, Mayrent SL "Cohort Studies" Chapter 2 in Hennekens CH, Buring JE, Mayrent SL (eds) Epidemiology in Medicine 1st edition, Boston Little Brown.
  - Doll R, Bradford Hill A. The mortality of doctors in relation to their smoking habits. Br Med J 1954;iii:1451-5.
  - Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years observations' on male British doctors. BMJ 2004; 328:1519.
  - Stampfer M, Colditz G, Willett W, Manson J, et al (1991) Postmenopausal estrogen therapy and cardiovascular disease. Ten year follow up from the nurses' health study. N Engl J Med 325; 756-762.

## What is a Randomised Controlled Trial?

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### *The basics*

A randomised controlled trial (RCT), also known as a randomised controlled clinical trial, is a study in which participants are assigned randomly to one of two or more arms (groups with different interventions) of a clinical trial. Occasionally, a placebo is used as one of the interventions, but, generally, if there is a recognised and accepted intervention that works (the "gold standard"), then a new drug, device or intervention is tested against this gold standard rather than against placebo. Where a gold standard drug or intervention exists, it would be unethical to randomise to a placebo and, by doing so, make an effective treatment unavailable to some participants. Generally, RCTs are conducted because there is equipoise (or uncertainty) about whether a new intervention is potentially better than an existing one. The trialists (the team of people that plan, conduct, supervise and analyse the results of the trial) start with the hypothesis that there is no difference between the two interventions (this is "the null hypothesis"). The purpose of the RCT is to reject or accept the null hypothesis. If they manage to reject the null hypothesis, they can accept the "alternative hypothesis", i.e., that there is a difference between the two interventions.

### *Blinding*

RCTs can be, but are not always, blinded. Blinding means that someone who plays an active part in the trial does not know what treatment (new intervention, gold standard or placebo) has been assigned to each participant. Trials can be single-blinded, double-blinded or even triple-blinded depending on how many types of people involved in the trial are blinded. For example, the participant could be blinded and not know what intervention they are assigned to. Or the medical doctor who deals with all the participants might not know to which intervention each participant is assigned. Or the statistician who reviews all the datasets and performs the statistical analysis might not know which group of participants has been assigned to which intervention. As you can imagine, if the participants are blinded, then there is less likelihood that they will complain of symptoms or side-effects that are known to be associated with either the new intervention, or the gold standard, or placebo. Similarly, a blinded doctor is less likely to assess patients in a biased way. To avoid the bias the statistical tests should be chosen prior to starting the RCT along with the rationale given for choosing them). Everybody has biases – even you!

### *Random Allocation*

RCTs by definition, randomly allocate participants to the different arms. This is designed to mimic chance, and to ensure that there is no difference between groups. A good trial published in a journal will show the characteristics of the various intervention groups summarised (usually in a table) and compared (often with p values and confidence intervals, though not always) to prove to the reader that there are no differences at baseline. Randomisation does not mean assigning alternate treatments to every second patient, nor assigning intervention A to patients who present on Mondays, Wednesdays and Fridays and intervention B to all others; if a well-meaning, but biased, physician wants his favourite patient to be assigned to intervention A he can tell that patient to come in on the day that intervention will be assigned; this is known as selection bias. Randomisation is designed to prevent biases, as well as to ensure "same-ness" between the assignment groups. The best method of randomisation is to use computer software to generate a sequence of random numbers, where each number refers to one of the interventions.

### *Sample Size Calculations*

Calculating the number of patients needed for a trial is important.<sup>1</sup> If you can show that a new intervention is statistically significantly better than the old intervention by randomising fifty patients, you can avoid the expense of randomising and treating one hundred patients (which would also be unethical if the new treatment was beneficial). On the other hand twenty-five patients might not be enough to detect a statistically significant difference, even if a difference truly does exist (this is a type II error). In other words the 'power' of the study was too low to show the difference. To avoid costly errors when planning a trial, trialists use a nomogram (e.g., Altman's nomogram<sup>2</sup>) inputting three pieces of information: the required level of statistically significant difference (usually to 0.05 or 0.01 level); a pre-determined difference between the interventions that would be clinically relevant; and the power of the study (the risk of making a type 2 error), which the trialists choose to set at a pre-determined level (often around 80%). This nomogram then calculates how many patients are needed to show this predetermined clinical difference, at the predetermined power and level of statistical significance. This is the total number of participants needed to complete the trial. Most trialists will try to recruit more than this, to allow for drop-outs during the study period. Sample sizing software can also be used to calculate the

optimal sample sizes, and simple algorithms can be used to produce sample size estimates.

The number of participants assigned to each individual intervention will also depend on the study design. The most common trial uses approximately the same number of participants in each arm, a 1:1 trial. But, if the trialists decide that they want two participants to receive intervention A for every one participant that receives intervention B; this is a 2:1 trial – then, advanced statistical input is required and your nomogram calculations are not appropriate. Interestingly, most large trials will not have exactly the same number of participants in each arm; this is due to the use of random number sequences. However, there are methods of randomisation available to statisticians that can be used to ensure equal numbers per arm of the trial, e.g., the use of 'blocking'.

**Table 1** Glossary of terms

Blocking	Randomisation occurs in groups (blocks) rather than based on individuals
Intention to treat (ITT)	all participants are analysed in their original groups even if drop out or cross over occurs
Nomogram	a graph used to calculate sample size
Sample Size	The number of participants required to detect a true difference between two interventions, if such a difference exists in the population
Type I error	A statistically significant difference is found between groups which is not true for the population
Type II error	No statistically significant difference is found between the groups though there is a real difference in the population; this is because the sample sizes were too small for the outcome being studied.

### CONSORT

The CONSORT statement<sup>3,4</sup> ([www.consort-statement.org](http://www.consort-statement.org), where CONSORT stands for CONSolidated Standards of Reporting Trials) was originally published in 2001 simultaneously in The Journal of the American Medical Association (JAMA), Annals of Internal Medicine, the Lancet and BMC BioMed Central, and an additional "Explanation and Elaboration Document"<sup>4</sup> explaining how to use CONSORT. The aim of CONSORT is to standardise reporting of the methods and results of RCTs. The rationale is that if the study is reported properly, it was probably conducted properly. Currently, most journals require that manuscripts reporting RCTs follow CONSORT guidelines. These guidelines include 22 points and a flow-diagram summarising the participation of patients during enrolment, intervention allocation, follow-up, and analysis in the RCT. One of the benefits of the flow-diagram is that readers can immediately identify if there was a significant drop-out in any of the arms of the trial (maybe in the new intervention arm, as participants found the side-effects intolerable, for example). Also, it helps the reader to identify if intention-to-treat analyses were really used to analyse both the efficacy and the side-effects profiles of the interventions being studied. Intention-to-treat analyses means that the effects of the intervention are studied in the group that was randomised to that intervention; so even drop-outs are still included in the analyses. If drop-outs are excluded from analyses, it could potentially over-estimate the treatment effect of the intervention as well as under-report the side-effects experienced.

### RCT Registration

Currently, anyone hoping to conduct a RCT is encouraged to register it. This helps to ensure that the results of "negative" as

well as "positive" trials are disseminated – the publication bias for "positive" trials is well recognised although, of course, it is unethical to conduct a trial and fail to disseminate the information, even if its results are "negative". Central registration of RCTs also helps to prevent duplication of trials studying a particular intervention and helps comparison of results, in the event of duplication. As a resource for identifying both "positive" and "negative" trials, it also facilitates authors of systematic reviews to identify all trials and to produce unbiased systematic reviews. Registration of trials when they begin is a requirement for publication of the results in certain journals, e.g., The British Medical Journal (BMJ). There are two large on-line sites for RCT registration; one is run by the National Institutes of Health in the USA ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the other is the Cochrane Central Register of Controlled Trials, run by the Cochrane Collaboration in the UK ([www.cochrane.org](http://www.cochrane.org)).

A properly-conducted trial is one of the highest levels of evidence, second only to systematic reviews, in the Hierarchy of Evidence<sup>5</sup> available to medical decision-makers today (i.e., you!). We hope that this tutorial helps you to evaluate RCTs and to make informed decisions. Maybe in the future, you will partake in, design or conduct your own RCTs! For further information on RCTs, see the sources below.

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### References

- Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of Beta, the type II error, and sample size in the design and interpretation of the randomised controlled trial. *N Engl J Med* 1978; 299:690-4.
- Altman DG. How large a sample? In *Statistics in Practice*, eds SM Gore, DG Altman, London. British Medical Association 1982. nomogram.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; 357:1191-1194.
- Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; 134:663-694.
- Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. *JAMA* 1995;274:1800-4.

### SUGGESTED FURTHER READING.

Websites: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
[www.cochrane.org](http://www.cochrane.org)  
[www.consort-statement.org](http://www.consort-statement.org)

#### Books:

Jadad AR. (1998) **Randomised controlled trials. A User's Guide.** London, BMJ Books, 1999.

Muir Gray JA. **Evidence-based health care: How to make health policy and management decisions.** London, Churchill-Livingstone, 2004.

Haynes RB, Sackett DL, Guyatt GH, Tugwell P. **Clinical Epidemiology. How to do clinical practice research.** USA, Lippincott, Williams and Wilkins, 2006.