

Statistics V: Introduction to clinical trials and systematic reviews

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Evidence-based medicine, research, and audit

Decisions regarding the care of patients must be made through the diligent, unambiguous, and thoughtful use of current best evidence. Evidence-based medicine is an exhortation to integrate individual clinical proficiency with the best available evidence from systematic research. The benefit and harm to patients are quantified using mathematical estimates derived from research on population samples. This mathematically quantified evidence base is then used to inform clinical decision-making in individual patients.

A recurring word in the definitions of evidence-based medicine is 'research' which may be defined as a systematic investigation which aims to increase the sum of knowledge. Research usually involves an attempt to test a hypothesis and may involve experiments on human subjects. Strict selection criteria are applied to patients entered into the research study which may involve the evaluation of a completely new treatment.

Research should not be confused with clinical audit which, according to a definition endorsed by the National Institute for Health and Clinical Excellence (NICE), is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery.

Designing a clinical trial

Observation

The first step in trial methodology results from observations made in clinical practice, the application of existing scientific knowledge, or both. For example, the density of opioid receptors on the peripheral nerve terminals of primary

afferent neurones increases in inflamed tissues. A clinician working with patients who have chronic knee pain secondary to osteoarthritis may speculate as to whether intra-articular injections of morphine in patients unsuitable for arthroplasty would benefit this group.

Generating a null hypothesis

The next step involves choosing the right research question, which in this case may be: is intra-articular morphine effective in reducing chronic pain from osteoarthritis? From the research question, a hypothesis is generated based on the available evidence. A hypothesis is a statement of belief to explain observed phenomena. The clinician believes that intra-articular morphine may be effective in reducing pain due to osteoarthritis. The null hypothesis would therefore be that intra-articular morphine is no better than placebo. On the basis of statistical analysis, the null hypothesis will be ultimately accepted or rejected.

Reviewing the literature

The next step is to perform a literature search to find out what is already known about the subject (the work may have already been done). This will probably involve searching a database like Medline which is compiled by the National Library of Medicine in the USA. Other databases and indexes include AMED, CINAHL, Embase, and Health Star. Many NHS Trusts will have librarians skilled in the use of these databases and it may be constructive to book a session with them.

A literature search reveals that intra-articular morphine has been used with good effect for acute pain after knee arthroscopy and that a small study found a beneficial effect in chronic knee pain but only followed patients up for 9 days.

Ethics approval

On the basis of the literature review and hypothesis, the next step is to complete the

Key points

Research tests a hypothesis and extends the boundaries of knowledge; audit is a quality control procedure in which structures, processes, or outcomes of care are compared against explicit best practice criteria derived from the best available evidence.

Clinical trials may be classified as retrospective (cross-sectional or case-controlled studies) or prospective (observational cohort or interventional studies).

Bias may occur in a clinical trial if the study groups are not similar in all characteristics except the variable(s) of interest. Bias may be reduced by random allocation of patients into study groups and blinding of patients and investigators.

Meta-analysis is a quantitative systematic review in which the data from multiple similar studies are pooled in an attempt to arrive at a valid statistical conclusion based on all the available data.

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online Integrated Research Application System (IRAS) which is in the process of replacing the National Research Ethics Committee (REC) form. Research in the NHS is under the auspices of the National Research Ethics Service which was launched in April 2007 and comprises the former Central Office for REC (COREC) and Research Ethics Committees (RECs) in England. RECs were formed as early as 1975 as part of NHS policy. Their remit is to act as an independent body which protects the rights of participants and the interests of researchers. New standard operating procedures for RECs came into force on March 1, 2004. These operating procedures were implemented to meet the EU Directive 2001/20/EC. The EU Directive only covers clinical trials of medicinal products, but the new procedure covers all RECs in the UK and all applications for ethical review of health-related research.

The IRAS form requires the investigator to explain in detail the study protocol and describes the objectives, design, methodology, and statistical considerations of the study. The organizational aspects of the trial are detailed such as the duration of the trial and the centres involved. The protocol also includes the background to the study and the rationale behind it with citations from the available literature. Ethical considerations, in particular the safety of participants in the trial, are an important component of the IRAS form. Details of the patient information sheet and the consent form are required. The manner in which the results of the trial will be disseminated must also be declared. The IRAS form should contain sufficient information, including an independent expert review of the subject and the trial design, for the committee to ascertain whether the study is a safe and worthwhile undertaking.

Essential to the IRAS form is a power calculation. A study must be adequately powered to minimize the risk of a type II statistical error. It would be unethical to perform an experiment where a beneficial effect was missed because of an inadequate sample size. Patients would have been put at risk and resources wasted. Good research practice would involve a statistician at an early phase of the experimental design.

Once the form has been completed, a telephone booking must be made to the central allocation system for trials involving medicinal products or multiple research sites for submission of the proposal in order to facilitate a 60-day answer. If the research project does not involve a medicinal product and is to be conducted at a single site, the application may just be submitted to the Local REC (LREC). If it involves a medicinal product, application has to be made also to the MHRA.

Once NRES and local Trust approval has been granted, the study takes place as documented in the protocol. Accurate record keeping is essential at this stage. On the basis of the results of the statistical analysis of the data, the null hypothesis is confirmed, rejected, or modified.

Types of clinical studies

Clinical studies may be retrospective or prospective. Quantitative systematic reviews and meta-analysis can be regarded as a form of

clinical trial also. Retrospective studies look backward in time and select study groups based on their exposure to a risk or protective factor in relation to an outcome established at the start of the study. They may be case–control studies or cross-sectional surveys. Prospective studies look forward in time and select a study group in order to ascertain what happens to them over time. Prospective studies may be interventional, in the case of randomized and non-randomized controlled trials, or they may be observational cohort studies.

Retrospective studies

Retrospective studies are useful in rare conditions when a prospective approach would take too long to accrue sufficient data. Retrospective studies are also useful when there is a significant lag period between exposure to a risk factor and the development of a disease. There are also situations where a prospective investigation may be unethical or where there is insufficient evidence to justify an interventional trial. Retrospective studies are relatively inexpensive and can utilize existing databases and registers.

However, there are disadvantages to retrospective studies. It may be difficult to obtain complete and accurate information on events which have occurred in the past, leading to recall error, and therefore introducing an element of bias. By definition, it is not possible to randomize the groups being studied and therefore their baseline characteristics will be different. This leads to the existence of confounding variables and makes proving causality difficult.

Cross-sectional studies/surveys

Cross-sectional studies examine either a random sample or all of the subjects in a well-defined study population in order to obtain the answer to a specific clinical question. They include surveys and studies which examine the prevalence of a disease.

Case–control studies

Patients with a specific disease or condition are selected and matched to a control group. The cases and controls are then compared for potential risk factors or causative agents implicated in the aetiology of the disease. An important source of bias in case–control studies is misallocation of cases into the control group, if the former do not meet specific diagnostic criteria defined by the researchers.

Prospective studies

Observational cohort studies

Cohort studies involve the selection of two or more groups and their subsequent follow-up over a number of years. The groups are selected based on the differences in their exposure to a particular agent and patients are followed up to see who develops the putative illness. The selection of a comparable group is one of the most difficult elements of a cohort study. Often complex statistical adjustments are made at the analysis stage in order to correct for

differences in the two groups at baseline. The most famous cohort study is probably that conducted by Austin Bradford Hill and Richard Doll who followed up a cohort of British doctors, dividing them up into four groups in terms of their smoking habits. Protracted follow-up demonstrated the causal link between smoking and lung cancer.

Randomized and non-randomized (cohort) interventional controlled trials

The fundamental feature of this form of prospective study is that it evaluates an intervention rather than merely observing two or more groups over time. In both randomized and cohort trials, the aim is to reduce systematic bias. Systematic bias may be defined as a variable that distorts comparisons between groups and erroneously influences decisions about them. The groups being compared should ideally only be different in terms of the intervention applied or the causative agent (smoking in the example above) being studied. Randomized controlled trials have important elements which aim to reduce systematic bias.

Avoiding bias in clinical trials

Randomization

Randomization ensures that each patient has a known chance of receiving each treatment but that the treatment they receive cannot be predicted in advance. Patients are neither consciously nor sub-consciously selected to be in a particular group. For example, in a trial aimed at evaluating early vs late tracheostomy insertion on ICU, randomization prevents a clinician from entering a patient into the early intervention group purely because he believes that the patient is likely to respond well to a prompt tracheostomy. Randomization ensures that the two groups are comparable and that the only difference between them is the intervention of interest.

Participation and selection bias

Patients in a randomized trial are not a random sample from the population of people with the disease but are a highly selected set of eligible and willing patients. The willingness to submit to a clinical trial introduces participation bias where simply taking part in a clinical trial can change the behaviour of patients and clinicians. Control groups in randomized controlled trials tend to fare better than patients receiving the same treatment who are not in a trial.

Selection bias occurs as a result of patients declining to take part in a clinical trial and therefore those who do take part may differ in some way. For example, patients who decline to take part in a trial of a new anti-hypertensive drug may also be less well motivated to change their lifestyle (diet, exercise, smoking, etc.) compared with those who do take part. The trial will therefore recruit self-selected individuals who differ from the wider population at whom the new drug is being targeted.

Allocation concealment

Allocation concealment ensures that the randomization sequence is not known or predictable in advance by the investigators. The use of sealed opaque envelopes opened only when a patient is actually recruited into a study is a robust method of avoiding allocation bias.

Blinding

Blinding of patients is an attempt to avoid performance bias where patients' perception of their health may be altered if they know they are receiving a new drug. This may lead to them reporting a spurious benefit. Whenever possible, investigators should also be blinded as to which arm of a study patients have been allocated in order to avoid observation bias. Knowing that the patient is on the treatment arm could also influence the manner in which they are treated.

Studies are termed double-blind when neither patients nor clinicians are aware of which study group patients have been allocated to. Analysis bias is avoided if the person assessing the intervention is similarly blinded.

Systematic reviews and meta-analysis

Systematic review is the formal process of identification, appraisal, and evaluation of primary research studies and other relevant research using strict criteria to draw conclusions about a specific issue. Meta-analysis is the statistical discipline of assimilating data from multiple similar studies to measure an overall effect using all of the available evidence.

Traditionally, the narrative review has been used as a means of providing a summary of the available evidence to guide clinical decision-making. However, narrative reviews are subjective and therefore prone to bias and error. They also often encompass an entire topic. Systematic reviews are more focused. They may be qualitative, where no pooling of data is possible because the individual studies are too dissimilar to combine, or they may be quantitative (meta-analysis).

The difference between a qualitative systematic review and a meta-analysis is that the latter represents a statistical integration of a number of studies which individually are either too small or give conflicting results. Although the studies need not have identical methodologies, they must be sufficiently similar such that the pooled data arise from reasonably homogenous study groups.

Although they can never be as statistically robust as large, randomized prospective controlled trials, meta-analyses are useful when a large enough study has not yet been undertaken or is unfeasible. The results of meta-analysis lead to an overall estimate of the effect of a treatment using all of the evaluable evidence, commonly expressed as a relative risk/benefit or odds ratio. Meta-analysis may also generate a number needed to treat (NNT), a number needed to harm (NNH), or both, which are clinically relevant measures.

Forest plots or blobbograms are used in order to show graphically the studies which have been included in the meta-analysis. They demonstrate the differences between studies and provide an

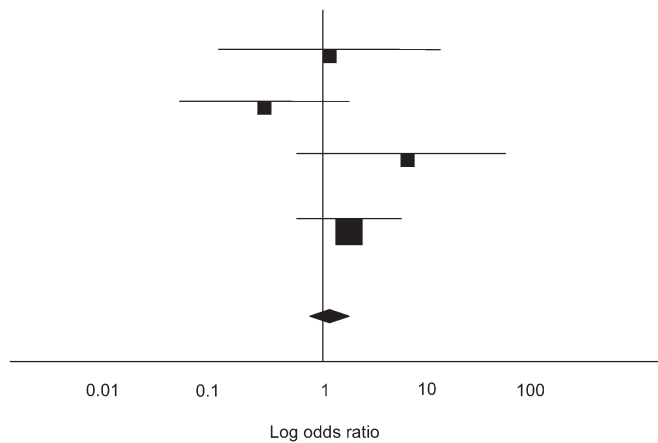


Fig. 1 Forest plot.

estimate of the overall result. The individual studies comparing two treatments are represented on the Forest plot in Figure 1. The x -axis represents the relative benefit of each individual study. The squares represent the point estimate of the difference between the study groups with respect to benefit or harm in each study and the width of the horizontal lines through them indicates the 95% confidence interval of this estimate. The size of the squares is proportional to the weighting each individual study is given, the main determinant of which is sample size. The y -axis is the line of no effect, that is, treatment is neither beneficial nor harmful with respect to controls.

In Figure 1, all the studies cross the line of no effect, suggesting either that there is no difference between the two treatments or that the sample sizes of the studies were too small to detect a difference (type II error). However, the diamond at the bottom of the forest plot represents the pooled data from all of the studies and demonstrates a narrow confidence interval which overlaps the line of no effect. Therefore, the conclusion of the meta-analysis is that there is no difference between the two treatments, which, although suggested by the individual studies, could not be confidently stated due to the small sample sizes involved.

Publication bias

Studies with positive or statistically significant results are more likely to be published by scientific journals compared with studies yielding negative trials (selection bias). Trials may not be included as a result of language bias if articles other than those published in English are not included. Data may be replicated in a meta-analysis, if it has been published in multiple articles (replication bias).

Funnel plots, where the magnitude of the treatment effect of individual studies (odds ratio) is plotted against either the sample

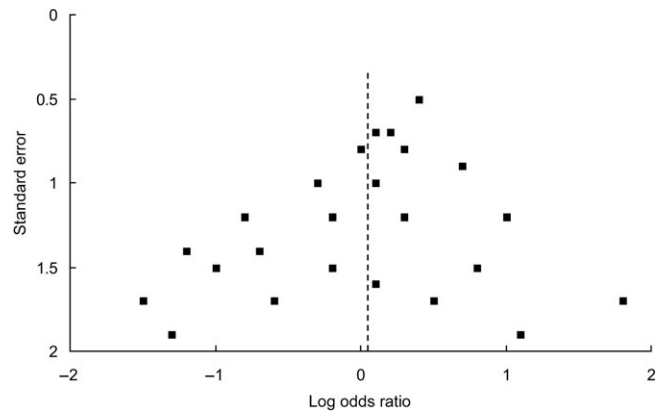


Fig. 2 Funnel plot showing the symmetrical inverted shape typical of a meta-analysis in which the source studies do not exhibit publication bias. The dotted line indicates the pooled estimate of the treatment effect from all of the included studies.

size or precision of the studies (standard error) may be used to detect publication biases. A symmetrical inverted funnel as shown in Figure 2 implies that the studies found are likely to be inclusive, whereas an asymmetrical plot suggests that small, negative, or neutral studies have been omitted. The dashed vertical line represents the pooled estimate of the treatment effect of all the included studies.

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Please see multiple choice questions 24–25