

## EVIDENCE-BASED MEDICINE

## (2) HOW TO APPRAISE A CLINICAL PAPER CRITICALLY

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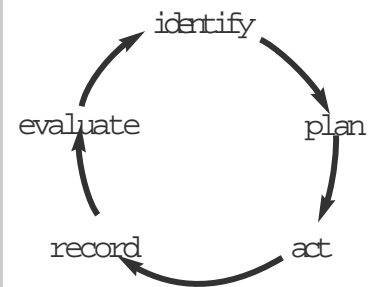
*Pharmacists are constantly being asked to make judgements about the relative merits of different drugs. However, in order to make these judgements we need the ability to discern good and poor quality information about medicines. This article looks at how to decide whether or not a research paper can be used with confidence*



### identify gaps in your knowledge

1. What is the first question you should ask when deciding whether or not to use a clinical paper to make a decision?
2. Can you list three possible sources of bias in a clinical trial?
3. What is the STEP acronym?

This article relates to the Royal Pharmaceutical Society's core competencies of "information systems and sources of information" and "decision making in relation to drug therapy" (see "Medicines, ethics and practice — a guide for pharmacists", number 25, July 2001, p104). You should consider how it will be of value to your practice.



Critical appraisal of clinical papers is not as difficult as you might think. Not only will this invaluable skill earn you more respect from your patients, colleagues and other health care professionals, it will enable you to become more involved with your primary care team. The large double-blind randomised controlled trial (RCT) is the gold standard in terms of assessing the value of a medical intervention, and any health care professional attempting to keep abreast of medical advances must be able to make sense of these. An RCT involves participants being randomly allocated to different groups with each group receiving a different intervention. Each group should be identical so that any effect can be attributed solely to the intervention.

The types of RCT that pharmacists are most likely to encounter are those which compare a drug with a placebo or those comparing two drugs. Imagine that a regular patient, Mr Jones, comes into your pharmacy unhappy that his doctor has refused to prescribe him a new drug, which the internet report he has in his hand claims is far superior to the drug he is currently taking. "It's probably because this new drug costs more!" exclaims Mr Jones, "What do you think?" Taking the internet information from him, you tell him that you will do some reading and get back to him. A few moments later the doctor rings to ask what you think about this new "wonder drug". You tell the doctor that you will read the trial behind the internet report and get back to him with your opinion. All that is left to do now is to download the trial from the internet and read it, but what are the factors that need to be considered?

### WHERE TO START

Trials are usually published in a set format: abstract, introduction, methods, results, discussion and conclusions. You need to know the questions to ask and what to look out for. It is always helpful to use a checklist when reading a clinical trial to ensure that you do not miss any of the key points. The National Health Service Critical

Appraisal Skills Programme (CASP) provides extremely useful checklists, for example "10 questions to help you make sense of a trial", but always start by asking two basic questions:

1. **Where is the trial published?** Just because a trial has been published, this does not mean that it is worth using. An RCT published in a peer-reviewed journal (eg, *BMJ*, *The Lancet*,) is considered to be the gold standard of information about the efficacy and safety of a treatment
1. **Is the trial sponsored?** Check for any reference to sponsorship of the research and to the author's affiliations (eg, to manufacturers), both of which might affect how the results are presented

### METHODS

The methods section is the most important part of a paper because it is an indication of how reliable the results are. In fact, this section should be read first because there is no point reading further if you know that the method used was seriously flawed.

**Is the precise aim of the study described?** It is important to pick out what precise question the trial was originally designed to answer (often called the primary outcome of the trial) and this should be defined in the paper. Once you have ascertained the precise aim, you should then check whether the study actually achieves it.

**Does the section contain details of all the steps taken to avoid bias?** The trial should be designed and conducted in such a way that nothing except the intervention influences the results. All possible mea-

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asures should be taken to reduce bias and the method should disclose what measures were taken. Examples are:

- 1 Methods used to achieve the random selection of subjects from the patient population and the random allocation of treatment should be stated
- 1 Both patients and investigators should be blind to the identity and allocation of the treatment (ie, a double blind study). If the trial was one for which blinding was not possible, you will need to think about the degree of influence this could have had on the results
- 1 Participants with identical characteristics (“matching”) should be used. It is important that you look for a description of all the baseline characteristics of the patients in the different treatment groups because these should be the same. This helps to ensure that any different effects between drug A and drug B are due to the different drugs and not to other differences between treatment groups
- 1 Except for the experimental intervention, all patients should be treated identically in terms of concurrent use of other drugs, advice given, methods of monitoring etc

**What were the inclusion and exclusion criteria of the trial?** Always check what type of patients were included in and excluded from the trial. You may, for example, find that the exclusion criteria for a trial are so strict as to eliminate effectively the majority of patients that would be seen in general practice. A classic example is if a trial only uses healthy 25-year-old males. Any data generated, considering the variation in pharmacokinetics, would not be applicable if you have to make a decision on a drug which would commonly be prescribed for a disease associated with the elderly. So in our scenario, does Mr Jones’ characteristics match those of the sample group?

**Was the group size and duration of the study sensible?** In clinical trials the number of participants should be large enough so that the researchers can be reasonably certain that the chances of detecting a beneficial effect or common adverse effect are high. In terms of study length, this also needs to be commensurate with the primary outcome sought. For example, a trial looking at the effect of teenage smoking on menopausal women would require a long follow-up. If Mr Jones would have to take the drug for long time, does the trial reflect long-term use?

**Is the new drug being compared with the gold standard?** A trial involving a new drug should, ideally, directly compare it with the gold standard already in use, and not with some obscure drug that is not commonly used in clinical practice.

**Are realistic comparative doses being used?** If a trial is directly comparing two drugs check to see if the doses being tested are realistic comparative doses. For example, you may be rather wary of a trial which seeks to compare the relative effectiveness of ranitidine 150mg *on* to omeprazole 40mg *od*.

**Is the variable selected for measurement really related to the answer being sought?** Surrogate markers are often used to save costs or time or simply because it may be impossible to measure anything else. Be wary of the use of surrogate markers in drug trials, particularly if the marker is a poor predictor of a hard clinical endpoint. For example, changes in bone mineral density and potential changes in rates of fracture do not have a true relationship. Fracture rates will also be affected by other factors such as the risk of a patient falling. There must be a clear and consistent link between the question at hand and any surrogate marker.

## RESULTS

The results of a trial need to be scrutinised in a similar way to the method.

**Statistical tests** You need to ask whether the result of the trial is a real effect or if it occurred purely by chance. Statistical tests are used to assess this. The result of the statistical test is expressed as a *P*-value. By convention a *P*-value below 0.05 is accepted as indicating a true and statistically significant result.

**Confidence intervals** Inferences based on random patient samples are uncertain because if a trial were repeated, different data would be obtained each time. To deal with this degree of uncertainty, confidence intervals (CI) are used. These represent the range of values within which the true value lies. It is important to look at the CI around each result. The narrower the range, the more reliable the results. Also, if the CI for the measures of the effects of two drugs overlap, then the study has failed to demonstrate a difference between the two. By convention, 95 per cent CI are used. This means that you can be 95 per cent sure that the true value for a population lies between the CI.

**How are the results expressed?** Results can be expressed as relative or absolute measures, but these may have little meaning in relation to clinical practice. Therefore the use of the terms like “number needed to treat” (NNT) can make these measures more understandable and relevant. NNT is the number of people who need to be treated to produce one additional successful outcome. Panel 1 shows how NNT is calculated.

**Are all patients accounted for?** The results section should be closely scrutinised to ensure that all the patients who entered the study are accounted for at the end. Some patients may drop out of a study because of side effects and ignoring these people could skew the results in favour of a drug, giving an overestimate of effectiveness. For this reason the final analysis of the results is considered to be more robust if it includes all the patients, even those who did not complete the study. Moreover, this more closely approaches a real life situation where some patients are not compliant with therapy, and is called an “intention to treat” analysis of the results.

**Surrogate markers versus hard clinical endpoints** Even though the primary outcome is that a new drug has an effect, is this primary outcome really one that is clinically valuable to patients? For example, if our internet report referred to a bisphosphonate drug trial, should the primary outcome be changes in bone mineral density (a surrogate marker) or changes in fracture rates (a hard clinical endpoint)? Clearly, from Mr Jones’ and the National Health Service’s point of view, it should be fracture rates.

**Statistical significance versus clinical significance** Always take a step back from the results and ask yourself whether a statistically significant difference in favour of a drug has any clinical value. If for example, the RCT compares two antihypertensive drugs, a difference of 1–2mmHg may be a statistically significant result, but this is unlikely to confer any significant clinical benefit to Mr Jones.

**Can the results be applied to the local patient population?** A trial conducted on a population of patients in southern China might possibly not be of much use when considering the potential effectiveness of a new drug in the UK.

### PANEL 1: TO CALCULATE NNT

A = the percentage of people who have the desired outcome in the treatment group

B = the percentage of people who have the desired outcome in the control group

A – B = percentage of people helped by the treatment  
Divide 100 by this percentage to give the NNT

For example,  
86 per cent of people treated with drug A in the treatment group showed an improvement; A = 86

82 per cent of people treated with drug B in the control group showed the same improvement; B = 82

A – B = 4

NNT =  $100 \div 4 = 25$

Therefore you need to treat 25 people with drug A instead of drug B for one extra patient to show an improvement

## action : practice points

1. Visit the CASP website, look at the 10 questions referred to in this article and apply them to a research paper. [www.phru.org.uk/~casp/resources/rct](http://www.phru.org.uk/~casp/resources/rct)
2. Next time you are visited by a drug company representative, ask for the fully published trial evidence of his or her claims and discuss its validity with your peers.
3. Visit the Medicines Resource Centre website ([www.mrc.co.uk/ctc/ctcIndex.htm](http://www.mrc.co.uk/ctc/ctcIndex.htm)) and read the *MeReC Bulletin* "The drug treatment of depression in primary care". Do you understand all the terms? If not, look back at the previous article in this series (PJ 15 June p839-41).

## evaluate

How could your learning have been more effective?  
What will you do now and how will this be achieved?

## DISCUSSION, CONCLUSIONS AND ABSTRACT

The discussion section of a clinical trial should be a methodical review of the results that leads logically to the authors' conclusions. The conclusions should reflect what the study has actually shown, rather than what the authors would have liked it to demonstrate. The conclusions should also address any inconsistencies or shortcomings in the trial.

Read the abstract and the discussion section of the paper last, not first. You may be surprised after you have read the full paper that you do not agree with the authors' summary of results and conclusions presented in the abstract. For example, the primary outcome of the trial may be defined but the trial may not have resulted in a positive primary outcome and the discussion and abstract may quietly put this to one side and concentrate instead on various secondary outcomes which the trial was not originally set up to address. Such results should be viewed with caution because the study would originally have been specifically designed to explore the primary outcome.

## FINAL CONSIDERATIONS

You might come to the conclusion that the clinical trial in question has been performed rigorously and is reliable. However, it may only answer one question and when it comes to forming an opinion about a drug in practice, a number of areas need to be looked at. These can be remembered using the STEP acronym<sup>1</sup>:

- 1 Safety: bear in mind that many trials (especially those on new drugs) may not give information about long term or serious side effects
- 1 Tolerability: what are the withdrawal rates from the trial compared to those from trials on a similar drug?
- 1 Efficacy: how does the drug compare with its most popular equivalent?
- 1 Price: is this drug affordable? Financial information does not normally appear in trials. Has a cost-benefit analysis been performed?

Going back to our scenario you should also consider other issues specific to Mr Jones using the new drug, such as the likelihood of interactions and whether or not the regimen required would be suitable for him.

## PRACTICAL TIPS

**Get some formal training and then practise** There are various sources of advice and training on developing critical appraisal skills. For example, you can access formal training through the NHS Critical Appraisal Skills Programme which runs regular courses throughout the UK ([www.phru.org.uk/~casp/index.htm](http://www.phru.org.uk/~casp/index.htm)). This programme will help you to distinguish between strong and weak evidence, and to use good quality evidence to support decisions (ie, the

basic skills). However, there is no substitute for practice. Perhaps you could set yourself a target of reading one clinical paper every week and arrange to discuss a paper with your peers.

**Use good independent sources of review** Our scenario involves a paper that has just been published and so it is unlikely to have been appraised by anyone else. However, decisions should not normally be made on the basis of one trial and to make a sound decision, looking at a systematic review of a number of trials is valuable. If you need to look at a paper that has been published for some time, or are asked to find out about the latest evidence-base in a wider therapeutic area, then it is always worth checking to see if anyone else has already done the work for you. For example, you may already regularly read the *MeReC Bulletin* or the *Drug and Therapeutics Bulletin*. For finding links to further sources of information, an excellent place to start is the links page of the CASP finding the evidence workshops (CASPfew) website (<http://libsun1.jr2.ac.uk/caspfew/sources.html>) which contains links to:

- 1 Journals, eg, *Evidence Based Medicine*, *Effectiveness Matters*
- 1 Sources of review, eg, Health Technology Assessment Reports
- 1 Books, eg, *Clinical Evidence*
- 1 Guidelines, eg, National Institute for Clinical Excellence
- 1 Databases, eg, Cochrane, Database for Abstracts of Reviews of Effectiveness (DARE)

For a review of sources of evaluated information on clinical effectiveness refer to MeReC.<sup>2</sup>

**Tap into the local networks** The regional medicines information network produces numerous high quality independent reviews of new drugs, and reports on critical appraisal of key papers. It may be worth contacting your local primary care trust (PCT) pharmacist to see if they have done any work on the particular area you are interested in. For example, has the drug been discussed by a local area drug and therapeutics committee or is it listed in any local PCT formulary?

## SUMMARY

With the wealth of good and bad information so readily available to patients today and the emphasis on evidence-based practice, in order to remain the expert, it is an essential skill for pharmacists to be able to form a justifiable opinion or make an appropriate decision based on scientific papers. The ability to evaluate information will also enable you to deal with the claims of drug company representatives and finally, with the advent of pharmacist prescribing, this is a skill that will carry the profession into the future.

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## FURTHER READING

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