

**Key words:**

Evidence-based Medicine; clinical trials; meta-analysis; systematic reviews; statistics

# Evidence-based medicine and clinical trials – from a clinical trials unit perspective

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### Abstract

It is a challenge to clinicians and policy-makers to determine which treatments are both efficacious and cost-effective. Evidence-based medicine is an essential part of healthcare policy and includes the processes of systematically identifying clinical evidence, appraising it critically and acting on the evidence of treatment effectiveness. However, interpreting the evidence is not straightforward and requires an understanding of statistics, clinical trials and meta-analysis. The aim of this paper is to describe the importance of evidence-based medicine from the viewpoint of clinical trialists and statisticians.

### Introduction

Evidence-based medicine (EBM) has been defined as the “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”, which is achieved by “integrating individual clinical expertise with the best available external clinical evidence from systematic research”.<sup>1</sup> EBM forms an essential part of healthcare policy, with clinicians required to assess a large evidence-base to support their clinical decisions on how best to treat their patients.

EBM includes the process of systematically identifying the appropriate evidence, appraising it critically and then synthesising and acting on the evidence. However, interpretation of the evidence is not straightforward: randomised controlled trials (RCT) are the gold standard for the comparison of treatments in a clinical setting, but it is not always easy to determine their quality, validity and relevance. Expert reviews and meta-analyses are additional sources of information on treatment efficacy and clinicians also need the skills to assess these in a reliable and un-biased manner.

### EBM and Critical Appraisal of Clinical Trials

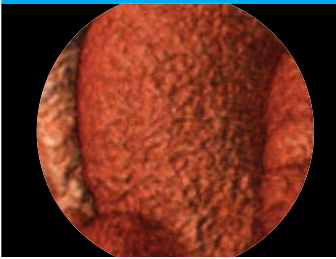
RCTs are the most reliable method for assessing treatment and non-randomised studies should be avoided. Non-randomised trials often lead to false-

positive results, and the treatment effect may be exaggerated in uncontrolled non-randomised studies.<sup>2</sup> A paper reporting the comparison of two treatments for acute myeloid leukaemia in the elderly illustrated the problem of using historical controls. The induction death rate for the 3-drug SAB regimen was found to be significantly lower than with the standard treatment of DAT (using historical controls) (15% versus 30%;  $p=0.00007$ ).<sup>3</sup> However, the SAB regime was ‘Same as Before’, meaning that both groups of patients received the same treatment (i.e. DAT). How can there be a significant difference between two groups receiving the same treatments? Possibly clinicians became better at managing DAT treatment with more experience (i.e. they managed the side-effects better) or supportive care may have improved over time, so that the outcome with DAT was significantly better than previously. Regardless of the precautions that are taken, comparisons using historical or other non-randomised controls are always likely to be subject to moderate biases, the exact size of which cannot be predicted reliably.<sup>2,4,5</sup>

Well-designed and properly executed RCTs are the gold standard for comparing treatments, but trial results should not be taken at face value without critically appraising the quality, validity and relevance. There are a variety of tools available to aid the clinician in this, including a critical appraisal tool adapted from two papers by Guyatt that provides a useful guide with ten systematic questions designed to assist in the appraisal process.<sup>6,7</sup>

#### Four main stages of the critical appraisal process of a clinical trial:

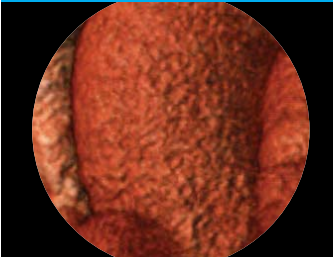
1. Is the study well designed?
2. Has the study been analysed correctly?
3. What are the results and have they been interpreted correctly?
4. Will the results help you locally?



**Natalie Ives** graduated from the University of Leicester (1995) with a first class honours degree in Mathematics. She then studied for a Masters in Statistics at the University of Sheffield. Her first post following university was as a statistician within the HIV research department at King’s College Hospital, London. After three years working in epidemiology, in January 2001, Natalie took up a post at the University of Birmingham Clinical Trials Unit. Here, she is the trial statistician for a number of Medical Research Council- and NHS-funded trials (PD MED, PD SURG and ASTRAL). Her interests include systematic reviews and she is co-author on a number of published data meta-analyses in Parkinson’s disease and melanoma.

## Evidence-based medicine and clinical trials – from a clinical trials unit perspective *continued*

Natalie J. Ives



### ***Is the study well designed?***

Is the study design appropriate and will it provide a reliable answer? Most trials use a parallel-group design where one or more treatments are compared to placebo/control or standard therapy and each patient receives only one of the study interventions (between group comparison). However, other trial designs may sometimes be more appropriate. In crossover studies, patients receive each study intervention in successive periods with the sequence of treatments determined at random (within group comparison), and because participants act as their own control, this design requires fewer patients than a parallel-group design. However, crossover trials are not always appropriate as they can only really assess short-term treatment effects in patients with stable and/or chronic diseases. In factorial trials, two or more interventions are evaluated separately, in combination and against a control. This design has been under-used in the past, but can be very efficient and allows the investigation of possible interactions between treatments, which is not possible in other trial designs.

Most trials are designed to determine efficacy based on observing a pre-defined difference between the two treatments. However, new treatments are often advocated with claims of equal effectiveness, but with fewer (or less severe) side-effects or better cost-effectiveness. In this case, the aim is to show that an experimental treatment is either equally effective (equivalence trial) or not worse (non-inferiority trial) than the active control. When designing equivalence or non-inferiority trials, a maximum allowable difference (or equivalence margin) needs to be specified.

In equivalence trials, the two treatments are considered equivalent if the observed treatment difference is no greater (in either direction) than this equivalence margin. In contrast, non-inferiority trials aim to show that an experimental treatment is not worse than an active control by more than the equivalence margin, with an

improvement of any size fitting in with the definition of non-inferiority. In reality, it is very difficult to prove that two treatments have exactly equivalent treatment effects, and these types of trials generally require larger sample sizes, so that equivalence or non-inferiority can be established with sufficient confidence. Furthermore, in trials aimed at detecting a pre-defined difference between treatments, failure to show a difference does not mean that the two treatments are equivalent.

The trial report should provide information on how the sample size was calculated.<sup>8</sup> Generally, trials are designed with the power set at either 80% or 90%, with 90% power meaning that if a real difference of the anticipated size exists, the probability of finding a significant difference between the treatments, with the given sample size, is 0.9. It is important to consider the magnitude of the difference that the trial is aiming to detect and whether the study is recruiting enough patients to answer the question reliably. Problems arise when there is an over-optimistic expectation about the likely treatment effect – the key question is then whether the possible treatment effect is a moderate one that is still worth knowing about, or if it is too small to matter. The medical literature is littered with trials that were too small to answer reliably the question of interest.<sup>9</sup> For example, in 55 trials of tamoxifen *versus* placebo for early breast cancer, only 6 studies reported a statistically significant survival benefit with tamoxifen. However, when the data from all 55 trials were combined in a meta-analysis, the results showed that tamoxifen reduces the risk of death by nearly 15% ( $p < 0.00001$ ) (Figure 1).<sup>10</sup> How can the evidence for the benefits of tamoxifen be so convincing if only 6 trials reported a statistically significant survival benefit? It has been suggested that the anticipated benefit from tamoxifen was unrealistically large, meaning that most trials were under-powered to detect the smaller, but clinically important, benefit of tamoxifen which became apparent when all the data were combined in a meta-analysis.

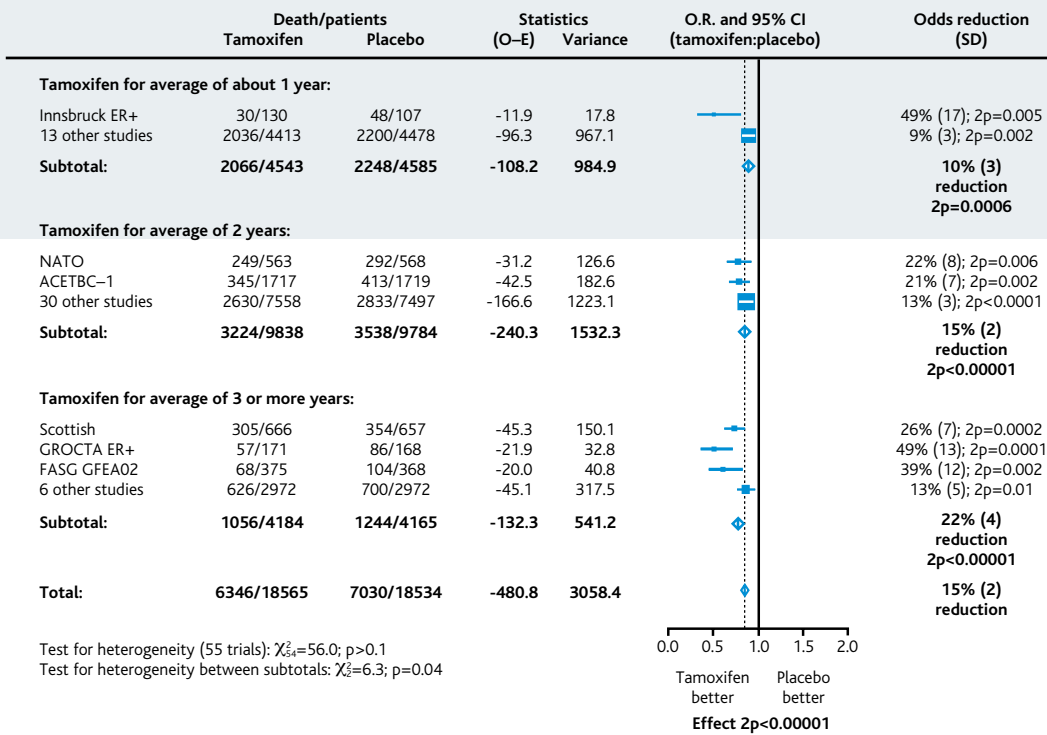
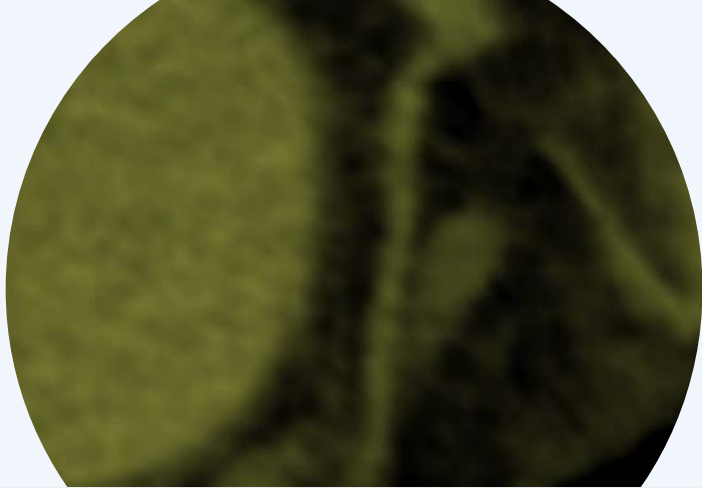


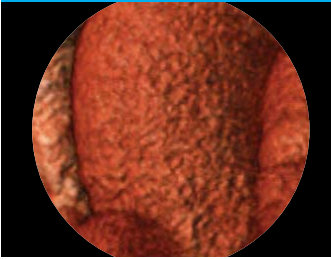
Figure 1. Mortality in 55 trials of tamoxifen versus placebo for the treatment of early breast cancer.

Although randomisation is vital in any trial, randomisation alone is not enough, and concealment of allocation is also important (i.e. the clinician should not be able to predict the next treatment allocation).<sup>11,12</sup> If there is any chance that the clinician can guess the treatment that the next patient will receive, then the decision to enter a patient into the trial may depend on the perceived treatment they would receive, which may result in systematic differences in the type of patients selected for one treatment rather than the other (selection bias).<sup>13</sup> For these reasons, randomisations based on date of birth or day of the week are seriously flawed. The treatment effect may also be exaggerated, with larger treatment effects reported from trials without adequate concealment compared to adequately concealed trials.<sup>14</sup>

The blinding of the study (i.e. did the patient and/or clinician know what treatment the patient was receiving?) is another important consideration especially in trials where the outcome could be influenced by the knowledge of the treatment (e.g. quality of life endpoints). Larger treatment effects have been found in non-blinded studies in comparison with their double-blind equivalent.<sup>14,15</sup> There is less need for blinding in trials where the outcome is not subjective (e.g. disease recurrence or death), and in some situations blinding may be difficult (e.g. surgery trials). Non-blinded studies should not however be regarded as poorer quality, but it is important to consider whether the outcome could potentially be biased by the patient (and/or clinician) knowing what treatment they are receiving (measurement bias).

# Evidence-based medicine and clinical trials – from a clinical trials unit perspective *continued*

Natalie J. Ives



**Consider the following when assessing whether the study is well-designed:**

1. What is the aim of the study?
2. Is the study large enough?  
Is the treatment effect realistic?
3. Is the randomisation procedure robust?
4. Is the study blinded? Is blinding necessary?
5. Are the intervention and comparator treatments appropriate?
6. Are the outcome measures appropriate?

**Has the study been analysed correctly?**

Having decided that the study is well designed, how can the validity of the results be determined? All trials should be analysed using the intention-to-treat (ITT) method: data on all randomised patients should be analysed according to the treatment allocated, regardless of whether they actually received this treatment or not. The reasons for ITT analysis have been discussed in

numerous papers,<sup>16-19</sup> but the main ones are that it minimises the potential for bias, avoids selective exclusion of patients and provides the most reliable assessment of treatment efficacy.

Are all randomised patients accounted for? Unfortunately, there will always be patients who withdraw from treatment or are lost to follow-up. It is important that this number should be minimised, as there are likely to be systematic differences in the types of patients who remain in the trial compared to those who drop-out (attrition bias).<sup>16,17</sup> The aim is to get complete follow-up on each patient, but if there are withdrawals, then hopefully the number (and reasons for withdrawal) are similar across each arm. The CONSolidated Standards of Reporting Trials (CONSORT) statement was devised to facilitate evaluation of the validity of a trial's results.<sup>20,21</sup> This checklist and flow diagram is aimed at improving the quality of reporting of RCTs, with trials submitted for publication expected to include the CONSORT flow diagram in the report (Figure 2).

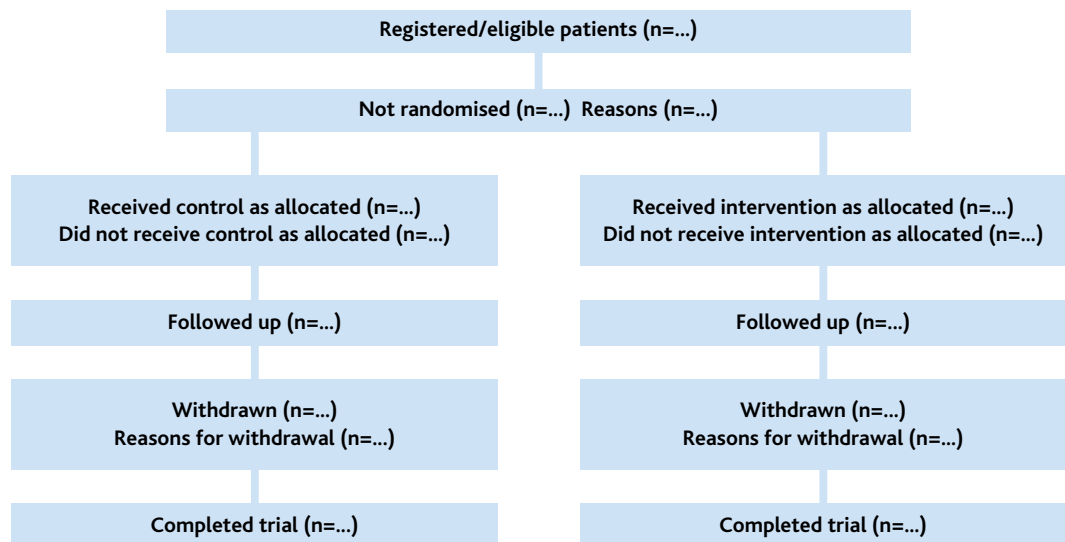


Figure 2. *CONsolidated Standards of Reporting of Trials (CONSORT) flow diagram.*



### What are the results?

There are various ways in which the treatment effect can be reported (relative risk, odds ratio, odds reduction, hazard ratio, mean change). However, alongside this point estimate for the treatment effect (which is just an average treatment effect), it is important to know how precise it is. Calculation of the confidence interval (CI) for the point estimate provides a measure of certainty and is essential for the assessment of treatment efficacy. The CI gives the range within which the true treatment effect is likely to lie; the wider the CI, the less certain is the estimate of treatment efficacy. The standard is to use 95% CI, which means that the true treatment effect will fall within this range of values 95% of the time (if the experiment was repeated 100 times, the treatment effect would be within this range 95 times out of 100). Therefore, both the point estimate and, more importantly, the corresponding CI are needed to determine treatment efficacy.

#### Consider the following when assessing the results of a study:

1. Was the trial analysed using an intention-to-treat analysis?
2. Are all randomised patients accounted for?
3. Were the data analysed using the correct statistical methods?
4. How are the results reported (i.e. odds ratio, hazard ratio etc.)?
5. How precise are the results? (i.e. are p-values and confidence intervals provided?)

### Will results help you locally?

The main purpose of critical appraisal is to determine whether the treatment could be used in clinical practice. Again, it is not sufficient to take the trial results at face value, points to consider include:

- Are the type of patients randomised into the trial the same as the patients that would be treated in

practice (i.e. did the trial have broad eligibility criteria and are the trial results generalisable)?

- Can the same treatment (especially in non-drug interventions like physiotherapy or occupational therapy) be provided locally?
- Treatment efficacy *versus* costs.

### EBM and meta-analysis

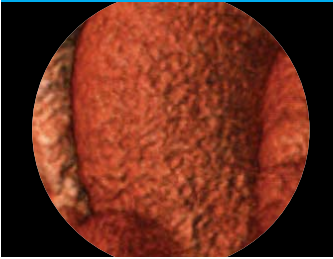
Meta-analysis is an evaluation of the totality of the evidence, which is achieved by bringing together all available data from all randomised trials that address the same question in patients with the same disease (i.e. trials of tamoxifen *versus* placebo in women with breast cancer as discussed earlier). But why perform meta-analyses? Most individual trials are too small to provide reliable answers on their own, and it is impossible to make decisions about treatments based on individual trial results. However, by using meta-analysis and combining data from a number of trials to obtain an overall treatment effect, it means that there is no undue emphasis on any particular study, be it positive or negative. As with clinical trials, the results of meta-analyses should not be taken at face value – the quality of a meta-analysis is dependent on the quality of the trials included in it and publication bias can be problematic.<sup>22</sup> Nevertheless, despite this, meta-analyses are essential for the assessment of treatment efficacy and provide the most reliable and un-biased assessment of the true treatment effect. It is important to note that the results of individual trials are unlikely to change clinical practice. However, by using meta-analysis and assessing the totality of the evidence, clinicians and healthcare policy-makers can make informed and evidence-based decisions about treatments more reliably (e.g. tamoxifen for breast cancer overview (Figure 1)).

### EBM and designing a clinical trial – ASTRAL

The development of any trial requires a similar process of reviewing the evidence as that described above. The Birmingham Clinical Trials Unit co-ordinates, the ASTRAL trial which compares angioplasty and/or stent placement

## Evidence-based medicine and clinical trials – from a clinical trials unit perspective *continued*

Natalie J. Ives



with medical treatment for atherosclerotic renovascular disease (ARVD). The trial is jointly funded by the Medical Research Council and Kidney Research UK.

### Reviewing the evidence

It is essential to check that the question has not been addressed in a previous trial or by ongoing research. If the question remains unanswered, then previous trials will help in defining the question and designing the study protocol – what were the study designs, what type of patients were included, what were the outcomes, what was the sample size?

A literature search of publications related to ARVD identified 95 potentially relevant articles, which was reduced to 5 RCTs (Figure 3).<sup>23-27</sup> The trials were all parallel-group designs, with 3 trials of angioplasty versus medical management, 1 trial of surgery versus angioplasty and 1 trial of angioplasty versus angioplasty plus stent. The aim of the two trials comparing surgical interventions<sup>23,26</sup> was to compare patency or re-stenosis rates. In comparison, the three trials comparing angioplasty with medical management assessed blood pressure response.<sup>24,25,27</sup>

The 3 trials comparing angioplasty with medical management showed that blood pressure and serum creatinine were improved in the angioplasty group, but the differences were not statistically significant. A meta-analysis of these trials confirmed these results, and concluded that previous trials were too small: while the combined data "exclude the possibility of a large improvement in renal function or hypertension after angioplasty, a moderate but clinically worthwhile benefit cannot be ruled out" (Figure 4).<sup>28</sup> Importantly, this meta-analysis and other review articles supported the need for further large-scale randomised evidence.<sup>28-33</sup>

### Clinical opinion

Finding that the medical literature supports the need for a trial is not sufficient. It is also important to canvas clinicians to assess their interest in the proposed question (and to aid in defining the question), as without the support of the clinicians who will be randomising patients into the trial, it is unlikely to succeed.

### Defining the question

A clear question has several key components:

- What patients are to be included?

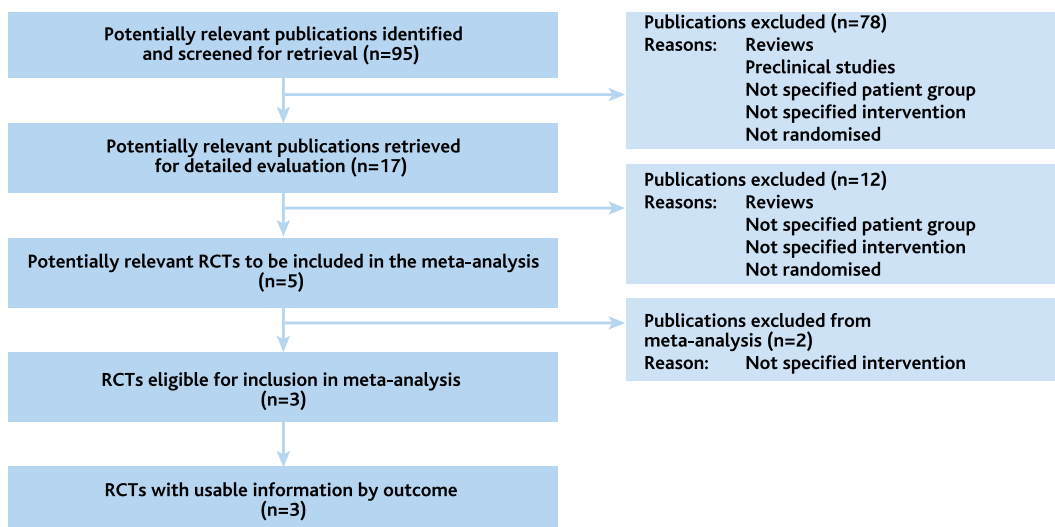


Figure 3. Improving the quality of reports of meta-analysis of randomised controlled trials: the QUORUM statement flow diagram (ASTRAL).

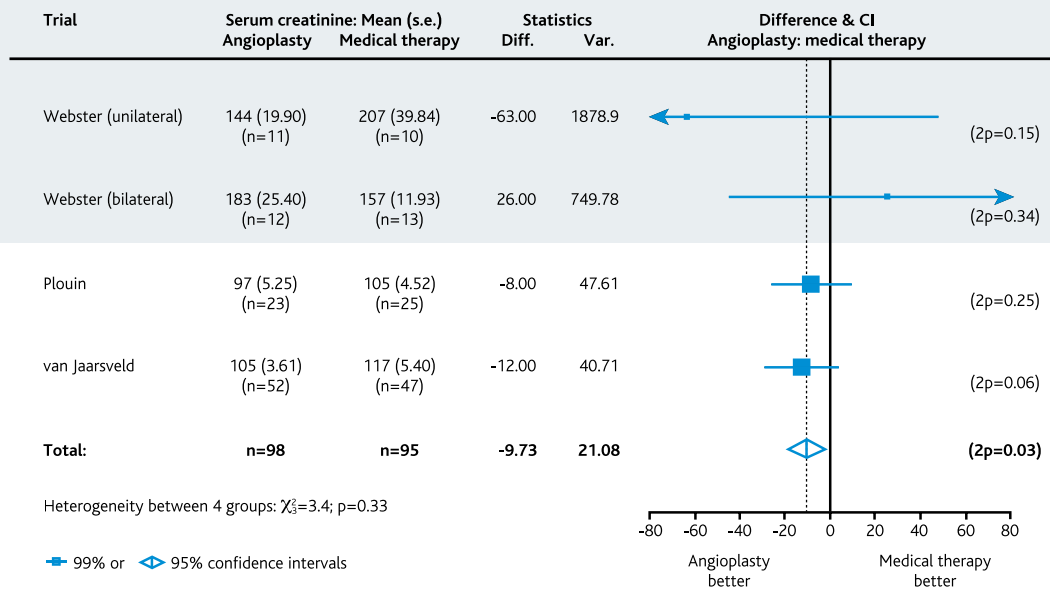
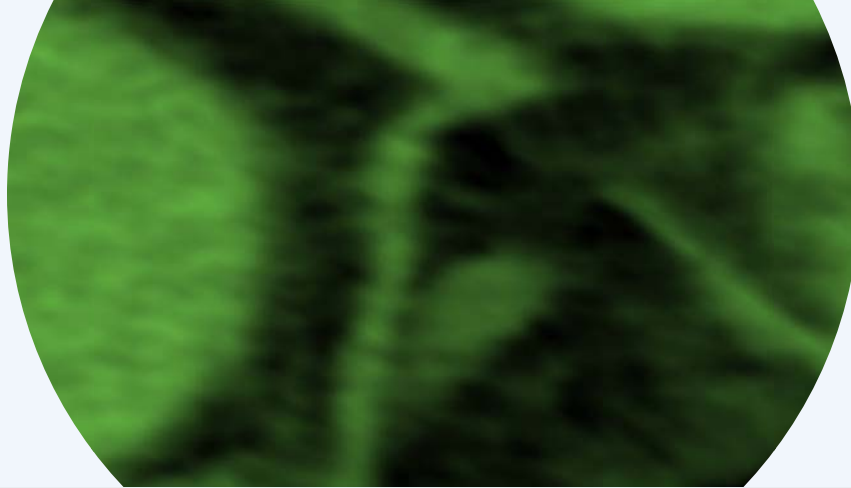


Figure 4. Meta-analysis of mean serum creatinine at 6 months.

- What are the treatments (intervention and comparator)?
- What outcomes should be collected?  
PICO rule – population, intervention, comparator, outcome(s)

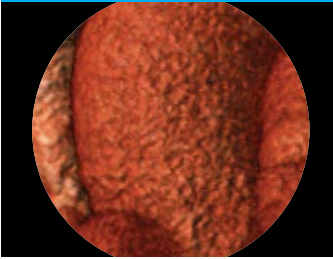
Previous trials recruited hypertensive patients with atherosclerotic renal artery stenosis and assessed the short-term benefit (longest follow-up in previous trial was 12 months<sup>27</sup>) of angioplasty on blood pressure. For the ASTRAL trial, a more heterogeneous population was sought (not just hypertensive patients). Since there is currently no clear evidence regarding the benefit of these interventions in preventing the progressive decline of renal function, change in serum creatinine was thought the most appropriate outcome. In addition, previous trials have compared angioplasty with medical management, but with a trend now towards inserting a stent following angioplasty, a comparison of revascularisation (angioplasty with or without stent insertion) versus medical management was thought more relevant. The box below summarises the ASTRAL trial design using the PICO rule of defining the question:

ASTRAL: PICO Rule of Defining the Question	
<b>Clinical problem:</b>	Does revascularisation delay progressive decline in renal function?
<b>Study design:</b>	RCT, parallel group design
<b>Sample size:</b>	1000 patients
<b>Follow-up:</b>	5 years
<b>Population:</b>	Patients with at least one ARVD lesion suitable for revascularisation confirmed angiographically
<b>Intervention:</b>	Revascularisation (balloon angioplasty with or without stent insertion)
<b>Comparator:</b>	Medical management
<b>Outcomes:</b>	Primary: Renal function Secondary: Blood pressure, renal events, cardiovascular events, death

The primary outcome in ASTRAL is the mean slope of the reciprocal creatinine plot versus time. The sample size was based on detecting a moderate reduction of 20% in this slope (i.e. reduction from  $-1.6 \times 10^{-3} \text{ l/}\mu\text{mol/year}$  to  $-1.28 \times 10^{-3} \text{ l/}\mu\text{mol/year}$ <sup>34</sup>), which gave a sample size (with 80% power) of

## Evidence-based medicine and clinical trials – from a clinical trials unit perspective *continued*

Natalie J. Ives



750 patients, which was increased to 1000 patients to allow for patient non-compliance and withdrawals.

Patients are randomised into the ASTRAL trial by either a telephone call to the central randomisation office or using the Internet randomisation service, thus ensuring concealment of next treatment allocation. Patients are allocated to either revascularisation or medical management, with the randomisation procedure based on the method of minimisation and stratified by baseline serum creatinine, glomerular filtration rate, percent stenosis, renal length and rate of disease progression.<sup>35,36</sup> Since the trial outcomes (serum creatinine, blood pressure, major events) are not subjective, it was not necessary to blind patients or clinicians to the allocated treatment.

In any long-term trial, there is the potential for new techniques or technology to be developed, which could have a detrimental impact on recruitment. Therefore, it is important that the trial design is pragmatic and adaptable to allow for such developments. Originally patients were eligible for the ASTRAL trial if they had at least one ARVD lesion suitable for revascularisation that was confirmed angiographically. However, during the course of the trial, following advances in the accuracy of imaging techniques, this was expanded so that patients could be randomised into the trial based on ARVD being confirmed by angiography, magnetic resonance angiography (MRA) or computed tomography (CT). Patients entered into the trial based on MRA or CT and who were randomised to revascularisation, were required

to undergo angiography prior to the intervention, so that the diagnostic accuracy of these imaging methods could be compared to the gold standard (angiography).

### **Where are we now?**

ASTRAL began recruiting in September 2000, and as of June 2006, 674 patients from 56 centres (including 3 in Australia and 1 in New Zealand) have been randomised into the trial. The trial remains open to recruitment until April 2007, although long-term follow-up of all patients will continue. The final analysis, once all patients have been followed-up for at least 6 months, is scheduled for early 2008.

### **Conclusion**

In an era of expensive treatments and limited budgets, clinicians and healthcare policy-makers have the difficult task of assessing the evidence-base to determine which treatments are both efficacious and cost-effective.

Evidence-based medicine and critical appraisal are an essential part of the assessment of treatment efficacy, as despite clinical trials being the gold standard for the comparison of many treatments in a clinical setting, not all clinical trials are of good quality. Interpreting the evidence and ensuring the assessment of treatment is performed in a reliable and un-biased manner is not straight-forward, and requires an understanding of statistics, clinical trials and meta-analysis. Clinical trial units have the experience of both clinical trial design and statistics to provide advice and support to clinicians undertaking clinical research.

### **Key Learning**

- Evidence-based medicine and critical appraisal form an essential part of healthcare policy
- Finding and, more importantly, correctly interpreting the evidence is not straightforward – it requires an understanding of statistics, clinical trials and meta-analysis
- Clinical trials are the gold standard for the comparison of many treatments in a clinical setting, but the rationale behind clinical trials is often misunderstood
- Clinical trial units have the experience of both clinical trial design and statistics to provide advice and support to clinicians undertaking clinical research



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