



## Cross-over trials: Painful lessons

by Richard Clark

### Pragmatic approach to pain trials

We like to think that modern Western medicine has a firm foundation in fact and proof, and yet there is debate about what constitutes proof. With regard to medical writing, we accept that the burden of proof is addressed in the form of clinical trials. The randomised double-blind placebo-controlled trial is generally accepted as the best proof for a particular drug, but is it always the best trial design?

Some years ago I had the onerous duty of trying to get the results of a ‘pragmatic’ trial accepted in the *British Medical Journal*. For reasons I won’t go into, a placebo-controlled, double-blind trial was not appropriate given that the two analgesics had different routes of administration such that a ‘dummy’ treatment would soon be unblinded. As many patients were suffering from severe chronic pain, a placebo group wasn’t ethical. Furthermore, the powerful analgesic effect of placebo in pain management is still not understood. We argued that comparing a new medication with the normal first-line treatment and using a cross-over trial design was the best approach, and eventually the manuscript was accepted and published [1]. Notwithstanding these arguments, the editorial (written by an expert in evidence-based medicine) was particularly scathing about the lack of double blinding [2]. Neither did he like patient preference as one of the outcome measures. As pain is subjective, patient satisfaction with their analgesic, or their preference for one analgesic over another, deserves special emphasis in pain management.

### Cochrane reviewers have their say

An audit of 43 major clinical guidelines with potential coverage of opioid-induced constipation formed part of a poster I was writing recently. Most of these guidelines gave some sort of advice on the management of this condition, but a notable exception was the Cochrane Review on opioid switching which gave no firm advice due to a lack of randomised controlled trials:

“Opioid switching is the term given to the clinical practice of substituting one strong opioid with another, in an attempt to achieve a better balance between pain relief and side effects. This is an established clinical practice for patients with cancer pain, but the evidence is based on case reports and uncontrolled studies, and *no randomised trials met the inclusion criteria for this review* [my italics]”[3].

This is so typical of the Cochrane reviewers. It takes 30 pages of text to tell us that not one study met their inclu-

sion criteria, and so they are not going to draw any conclusions (except that they cannot draw any conclusions). If your parent or grandparent was in severe pain or having very unpleasant side effects while receiving an opioid, would you tell the clinician not to try switching them to another opioid because the Cochrane review didn’t draw a conclusion on the subject? Of course not!

### Evidence-based medicine protagonists wanted for parachute trials

This puts me in mind of the (not entirely serious) call for randomised double-blind trials of parachutes [4]: The authors wanted to determine if parachutes were effective in preventing death or major trauma “related to a gravitational challenge” by conducting a systematic review of randomised controlled trials. They were unable to identify any randomised controlled trials of parachute intervention. Thus, they concluded that:

“As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence-based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organised and participated in a double-blind, randomised, placebo-controlled, cross-over trial of the parachute.”

### Irrational beliefs

To take the other side of the argument, we sometimes tend to have some fairly irrational beliefs, even when there is overwhelming scientific evidence to oppose this irrationality. Many doctors are afraid of prescribing opioids because of a perceived danger that proper medicinal use of these analgesics leads to a danger of physical addiction. In fact, this is very rare. On the other hand, many more dangerous drugs are sold without prescription. In the UK alone, non-steroidal anti-inflammatory drugs cause about 2000 deaths per year due to gastrointestinal damage that they can cause [5]. In the US this figure reaches 16,500 deaths per year [6].

The reaction to the introduction of the measles, mumps and rubella (MMR) triple vaccine is another example of irrationality. The mass of evidence shows the safety of this formulation, but many people did not want their children vaccinated with it, instead preferring single vaccines (despite

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the lack of any evidence that single vaccines are any safer). Many didn't vaccinate their children with any of these component vaccines in any form. One study in 12 children had alleged a potential link between autism and the MMR vaccine [7], and together with media hype and the perceived rise in incidence of autism, this led to low levels of MMR vaccination in the UK. Though the weight of evidence is skewed dramatically in favour of vaccination, many parents might feel worse if they *actively* did something causing their child to be ill (i.e. vaccination followed by autism) rather than being passive (no vaccination and then the child gets measles, mumps or rubella). This is understandable but not very logical. Interestingly, even a Cochrane Review concluded that "There was no credible evidence behind claims of harm from the MMR vaccination", so you know that the evidence in favour of MMR has to be overwhelming!

### A logical approach to causality?

We need to take a more logical approach to causality. The causal criteria set by Sir Austin Bradford-Hill are very useful in this respect [8]. These are: (1) *strength* of association, (2) *consistency* of observation, (3) *specificity* of association, (4) *temporality* of the relationship, (5) existence of a *biological gradient*, (6) *plausibility* of causative relationship, (7) *coherence* of causative relationship with existing understanding, (8) *experimental* demonstration of cause and effect by manipulation of suspected cause and (9) *analogy* to an existing recognised cause. However, I'm assured that it is not as simple as this (though it seems complicated enough already!). Bradford-Hill never used the term 'criteria' and he explicitly stated that he did not believe any hard-and-fast rules of evidence could be laid down, emphasising that his nine "viewpoints" were neither necessary nor sufficient for causation. Nevertheless, as a non-statistician myself, these criteria seem pretty useful, even if they just form a framework for discussing evidence regarding a potential causative relationship. To come back to the MMR example, parents are worried that there is an association between this multivalent vaccine and autism based on temporality (Bradford-Hill criterion number 4). This is clearly just one facet of the logical approach to causality and is not enough on its own, particularly in small numbers of vaccinated children.

### Tui Na

Western medicine does not have all the answers. So, many people (myself included) have used 'alternative' medicines or therapies—in the absence of scientific proof—in preference to mainstream medical treatments. Why is that? The usual advice about chronic back pain has changed from 'lie very still on a hard surface and don't move' to 'take painkillers and perform your normal daily activities'. I'd had a bad back for quite a while, and neither of these approaches worked very well. Chiropractic treatment helped a bit, but recently I've tried the exotic-sounding Tui Na, which has been remarkably effective. Essentially, this

is a little-known branch of Chinese medicine that dates from about 1700 BC that includes massage of soft tissues (muscles, ligaments and tendons), accupressure techniques and musculoskeletal/ligament manipulation. No doubt the Cochrane reviewers would not be pleased. It would be great to have a randomised cross-over trial of Tui Na with 'usual care', but I'm not going to wait for that.

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## Queuing strategy for medical writers

In that awkward pause in a buffet queue, after you have been asked what you do for a living and have replied 'medical writer', you might consider filling the silence with a few facts from Word Trivia<sup>1</sup> as follows:

I am (which by-the-way is the shortest complete sentence in the English language) a medical writer. Did you know that 'hillypilly' is one of the two longest words in English consisting only of letters with ascenders, descenders and dots in lower case, 'asthma' begins and ends with a vowel but has no other vowels in between, 'abstemious' has five vowels in order, the plural of 'mouse', the rodent, is 'mice' and the plural of a computer 'mouse' is 'mouses', the word 'stifle' is an anagram of 'itself', the longest words that are reverse images of each other are 'stressed' and 'desserts'—at this point you might find that your stressed audience has made for the desserts leaving your field free for the starters.

1. <http://users.tinyonline.co.uk/gswithenbank/wordtriv.htm>