What are the implications of optimism bias in clinical research?

Two decades ago, Peter Gøtzsche drew attention to the issue of citation bias: studies of new treatments are more likely to cite previous studies reporting positive results than equally valid studies with disappointing results.[1] John Ioannidis[2] has recently provided compelling evidence for the persistence of this phenomenon in a study of 49 reports of frequently-cited original clinical research. While almost all of the reports (n=45) claimed to show intervention effectiveness, in almost a third of cases (n=14), subsequent studies yielded estimates of effects that were either weaker than (n=7), or actually contradicted (n=7) the original studies.

Citation bias is, however, just one manifestation of what might be called optimism bias—unwarranted belief in the efficacy of new therapies. It has been shown that optimism bias is more likely to be promoted by research sponsored by industry than it is by publicly-funded research.[3] This difference reflects either biased under-reporting of less favourable studies, or inappropriately selected comparators.[4] More recently, it has been suggested that optimism bias is likely to be encouraged not only by selective reporting of complete studies, but also by selective reporting of outcomes within studies,[5] and by early stopping of studies.[6]

Optimism bias has several serious implications. One is the creation of unrealistic expectations, for both patients and clinicians, of the likely benefits of new treatments in randomised trials. For example, in the early 1990s, clinicians participating in a trial of a new radiotherapy treatment for head and neck cancer were asked for their expectations of the likely outcome. Their responses revealed a high level of optimism,[7] the consensus being that the new treatment would reduce mortality by around 30%. In the event, the trial found no evidence that the new treatment was an advance.[8] Furthermore, an analysis based on a cohort of 57 radiotherapy trials done between 1968 and 2002 and involving nearly 13 000 patients has shown that innovative treatments are as likely to be inferior to established treatments as they are to be superior (odds ratio for mortality 1·01, 95% CI 0·97–1·06).[9]

This example highlights one way of countering optimism bias: to present systematic reviews of relevant evidence to patients and clinicians involved in randomised trials. Despite its ethical and scientific benefits, this practice is not yet done routinely. One result of this indefensible situation is that some trials are less well designed than they should be, and others are frankly unnecessary.[10] Optimism bias could also be countered by using quantitative methods to assess the inherent credibility of new findings.[11]

Peter Gøtzsche (left), John Ioannidis (middle), David Spiegelhalter (right)

Optimism bias raises a crucial empirical question: what is the prior probability, on average, of a proposed new treatment being superior to established treatments?[12] Remarkably, there has been very little research done to address this question. One obstacle is the need to base analyses on cohorts of studies defined before their results are known, and for which all results become available, even if not through formal publication. Some such cohorts exist for publicly funded trials. However, we are not aware of any reports of such analyses of cohorts of commercially funded trials. The available data suggest that new treatments are equally likely to be inferior to standard treatments as they are to be superior.[12–15]

This finding is consistent with the concept of uncertainty on which ethical patient allocation in clinical trials is supposedly based. Yet it does not seem to be reflected in the beliefs of clinicians considering becoming involved in clinical trials. At a recent UK Clinical Research Collaboration meeting, David Spiegelhalter emphasised that optimistic distribution of predictions has emerged repeatedly when clinicians have been asked for their views.

Optimism about treatment can be helpful in the clinical setting.[16] Nevertheless, clinicians need to be aware that optimism is usually both unwarranted and counterproductive when there is uncertainty about

the effects of treatments, and of the resulting need to address this uncertainty in clinical trials. In these latter circumstances, optimism bias is a serious problem. It runs the risk of deterring participation in clinical trials designed to reduce genuine and important uncertainties about the effects of treatments, and of discouraging replication of apparently promising early studies. Until its persistence is addressed there must remain doubt about whether clinicians involved in randomised trials are genuinely observing the ethical requirement of uncertainty.

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Rheumatoid arthritis: the goal rather than the health-care provider is key

Inflammation and subsequent damage of the joints in patients with rheumatoid arthritis (RA) leads to disability. Many patients develop joint damage during the first several months after onset of disease,[1] and treatment is therefore aimed at suppressing the inflammation early and preventing development of joint destruction.[2] Shortly after onset, the patient is particularly susceptible to treatment, and management during this period is critical to the outcome.[3] Tight control of disease activity is superior to routine care in patients with short duration of disease and active disease.[4,5] (figure). Deborah Symmons and colleagues have recently studied treatment and care models of RA patients with disease lasting longer than 5 years.[6]

Symmons and colleagues aimed to find out whether aggressive care would be more effective than symptomatic treatment in increasing physical function and reducing signs, symptoms, and damage. Two types of care associated with two types of treatment were compared. Patients given symptomatic treatment were given the telephone number of a nurse, were interviewed by the nurse to establish symptom control every 4 months, and were seen by a rheumatologist once a year. The treatment was adjusted according to a prespecified schedule. Disease-modifying antirheumatic drugs were used, but not in combination. The aggressively managed patients were seen by a specialist every 4 months, and treatment was aimed at controlling symptoms as well as clinical and laboratory signs of inflammation (such as maintaining C-reactive protein below twice the normal upper limit). Combinations of disease-modifying antirheumatic drugs, ciclosporin, or cyclophosphamide were allowed. The study was done before the advent of biological treatment.

There was no significant difference in the progression of functional disability, as measured by a