Per protocol analysis useful in certain situations

By including patients who did not receive the treatments being compared, intention to treat analysis usually underestimates (or more rarely overestimates) the true differences between the treatments' beneficial and adverse effects (2). This is compounded when a substantial proportion of patients do not receive the treatment as planned after randomisation (2). In the hypothetical example of treatment for carpal tunnel syndrome, more than half of the patients in the wrist splint group who obtained symptomatic relief (27 out of 52) did so following surgery. If intention to treat analysis alone were performed, the efficacy of splinting would be greatly overestimated, and conversely, the efficacy of surgical treatment underestimated.

Per protocol analysis is also justified when verifying a vaccine's true protective efficacy against a disease. Only the results from vaccinees who received all doses of the vaccine are relevant.

However, regardless of the intervention being tested, the greater the number of patients excluded from the per protocol analysis, the greater the risk of bias in the analysis.

In non-inferiority trials, in which the objective is to verify that new treatment A is no less effective than an older treatment B, the choice between intention to treat and per protocol analysis is complex and mainly depends on the effect of treatments, the number of protocol deviations and what caused them (5). When in doubt, it is preferable to have access to both analyses and to draw conclusions based on critical appraisal of these two analyses.

When evaluating the adverse effects of a treatment, it is useful to examine a per protocol analysis that only takes into account patients who actually received the treatment in question. The weakness of intention to treat analysis in this situation is that it includes patients who were not exposed to the treatment.

Complementary information

Because intention to treat analysis preserves the similarity of the groups created by randomisation, it is usually the first approach to consider. Inclusion of the results of an intention to treat analysis in the clinical trial report is one indication of high-quality trial methodology. Intention to treat analysis is also the most suitable analysis for assessing the efficacy of a treatment strategy in routine practice.

Per protocol analysis can provide useful additional information about the treatment's true beneficial and adverse effects when it is taken in an optimal manner. It is also useful in some non-inferiority trials. But the greater the number of patients who are excluded from the per protocol analysis due to protocol deviations, the greater the risk of bias in the analysis. And when a per protocol analysis is performed retrospectively, to demonstrate a difference that was not detected by intention to treat analysis, its conclusions carry no weight at all.

Selected references from Prescrire's literature search.

1- Chevalier P "Analyse en intention de traiter" *Minerva* 2010; **9** (2): 28.
2- Cucherat M "Le contrôle du biais d'attrition: analyse en intention de traiter et remplacement des données manquantes" August 2009. www.spc.univ-lyon1.fr/polycop/ accessed 17 April 2011: 8 pages.
3- Hollis S and Campbell F "What is meant by intention to treat analysis? Survey of published randomised controlled trials" *BMJ* 1999; **319**: 670-674.
4- Nüesch E et al. "The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study" *BMJ* 2009; **339**: b3244.
5- Sanchez MM and Chen X "Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat" *Stat Med* 2006; **25** (7): 1169-1181.
6- Chevalier P "LOCF ou pas LOCF? Quand les données manquent" *Minerva* 2008; **7** (8): 128.

Translated from ***Rev Prescrire*** **September 2012; 32 (347): 693**

Neuroscience: reporting bias

● **Risk of overmedication and adverse drug reactions.**

What are the main causes of mental health problems? Are they mainly due to biochemical causes, and therefore best treated with drugs? Or are they mainly caused by environmental factors, requiring psychological or socioeconomic approaches? Biased reporting of study results appears to be skewing the evidence in favour of biochemical causes (1,2).

The mainstream press echoes the scientific literature. A group of neurobiologists examined articles on attention deficit hyperactivity disorder (ADHD) published in the lay press and in the scientific press. Their analysis focused on articles about a possible genetic cause for ADHD and a possible link between ADHD and dopamine deficiency (1,2).

This study showed that the mainstream press clearly overstated the role of genetic factors as well as the link with dopamine. But this bias was already present in the original scientific articles.

In fact, the authors found many examples of bias in the scientific publications they analysed: major discrepancies between results and conclusions; firm conclusions in the abstract while important limitations are only presented in the body of the article; inappropriate extrapolation of preclinical findings as if they represented treatment prospects (1,2).

The authors explained this reporting bias by the fact that the mention of therapeutic applications increases the likelihood of an article being published in a prestigious scientific journal, as well as the chances of obtaining research funding.

They stress that the phenomenon is not restricted to ADHD, but is observed throughout the field of neuroscience, particularly in depression (1,2).

Bias that leads to overmedication. Both the scientific and lay press exaggerate the role of biochemistry and genetics in mental health problems. As the study's authors point out, reporting bias skews the evidence towards drug treatment at the expense of psychological or social approaches (1,2).

Patients risk being exposed to overmedication, which has limited or no efficacy, but causes undeniable adverse effects.

Selected references from Prescrire's literature search.

1- Gonon F et al. "Misrepresentation of neuroscience data might give rise to misleading conclusions in the media: the case of attention deficit hyperactivity disorder" *Plos One* 2011; **6** (1). www.plosone.org accessed 2 May 2012: 8 pages.
2- Gonon F "La psychiatrie biologique: une bulle spéculative?" *Esprit* November 2011: 54-73. http://esprit.presse.fr accessed 15 June 2012: 20 pages.