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The uncertainty principle

For a randomised trial to be ethically valid there should be uncertainty about which of the treatments concerned is better. If there is complete uncertainty, there should be an equal chance of either outcome and half of all trials should favour the new treatment and half the control treatment. Deviation from this equipoise would suggest either bias or poor quality trials. (This argument is, of course, an absolutist argument in that it insists on complete uncertainty. You might, perhaps, expect some loading in favour of new treatments as such treatments are often developed because there are good theoretical reasons to think that they might be better than standard treatments.) A report from the USA (Benjamin Djulbegovic and colleagues. *Lancet* 2000;356:635-8) has shown a heavy loading in favour of new treatments in trials sponsored by commercial firms.

They analysed 136 published randomised trials of treatment for multiple myeloma. Ninety-five were funded by government or other non-profit organisations and 35 had commercial funding (six were of unknown funding). The overall trial quality was poor but commercially funded trials were slightly better. In general, equipoise was maintained, 56% of trials favouring the tested treatment and 44% the control treatment. However, there was a distinct difference between commercially and non-commercially funded trials, with 74% of the former and 53% of the latter favouring the tested treatment. Trials funded by non-profit organisations were much more likely to have active rather than placebo or untreated controls.

Trials sponsored by the pharmaceutical industry are usually well conducted, but may have inferior control groups and may seem biased in favour of the tested treatment. But the industry will no doubt argue that their products are designed so carefully that by the time they reach the stage of clinical trials they are likely to be effective. However, although on theoretical grounds a new drug may have advantages over previous drugs, pharmaceutical companies must arrange randomised trials to prove it. That does not seem to me to involve any compromise of ethical principles. Perhaps in unusual circumstances, when there are very good grounds for suspecting that a new treatment will be effective, there is no effective treatment already available, and the condition being treated is very serious, it might be ethical to perform a non-randomised trial with historical controls, but randomised trials will surely remain the general rule.

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