
How can clinical trialists serve the needs of clinicians and patients more effectively?

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STEPHEN HOLGATE

THE NEED FOR TRIALS REFLECTING THE REAL WORLD OF CLINICAL PRACTICE
10.40 – 11.00



BIOGRAPHY

Stephen Holgate is an MRC Clinical Professor of Immunopharmacology at the University of Southampton with a specific research interest in asthma and allergic disease, about which he has published over 800 peer-reviewed papers and 45 books. He is Chairman of the MRC Physiological Systems and Clinical Sciences Board, the Science in Health Group of the Science Council, the Government Expert Sub-Group on Air Quality, and a member of the Royal Commission of Environmental Pollution.

ABSTRACT

The randomised control trial (RCT) is accorded pre-eminent status in the hierarchy of evidence. Especially for new pharmaceutical or biotechnology products, however, most RCTs are "efficacy studies", conducted in highly selected patient populations chosen to give the greatest chance of showing efficacy. In asthma, where clinical trial patients represent ~2% of the real world asthma population, selection criteria are often so stringent that recruitment into trials can be close to impossible (1).

About 20% of people with asthma smoke cigarettes, yet they are always excluded from Phase II and III efficacy studies. As a consequence, it has only recently been discovered (2) that asthmatic patients who smoke do not respond to inhaled corticosteroids (introduced for this disease 40 years ago) but do respond to leukotriene modifiers. Patients are often selected on the basis of their bronchodilator response to an inhaled β_2 -agonist (eg salbutamol) with patients not achieving >15% increase over baseline being rejected. While used to define asthma as a reversible airways disorder, such stringent criteria would select in favour of "responders" if the RCT was being used to investigate a short or long-acting β_2 -agonist (LABA) (3). Many patients with asthma do not achieve such marked bronchodilator response and are therefore excluded from studies. In trials used to derive asthma management guidelines (GINA), only 6% of asthmatic patients would be represented (4).

Children and the elderly are especially neglected in clinical trials – prescribing being extrapolated from efficacy studies in otherwise healthy asthmatic adults (5). Examples include the lack of efficacy of LABAs in children's asthma and concerns over inhaled corticosteroids on growth and bone maturation in children, especially if started at a very early age (6), for which evidence of a beneficial influence over the disease's natural history is lacking (7). Adherence to therapy is a special concern in adolescents and children (8), and in the elderly (9) using inhalers. In practice, most patients do not take their inhaled therapy as prescribed, often using it intermittently and in too high or too low a dose. Guidelines use average data to discriminate between the effects of one drug compared with another, yet for both drugs there are "responders" and "non-responders" (10). Emphasis on meta-analyses, in which large numbers of trials are combined, can lead to erroneous conclusions, especially if data referring to different age groups are combined, or trials excluded for theoretical rather than practical reasons. A good example is the rejection of sodium cromoglycate (a safe anti-asthma drug with proven inhibitor of effects on the allergic inflammatory response) by the Cochrane review, and subsequent asthma management guidelines, based on analyses that are now being challenged (11).

Finally, the setting, the practitioner, the patient's social and family circumstances as well as co-morbidities can all influence treatment outcomes (13). These non-specific (placebo) and

confounding effects are all subtracted to reveal "efficacy" as the specific treatment effect, but in a complete system such as a diseased human being, non-specific and other effects can greatly influence the response to the specific therapy (14). Placebos are not ineffective treatments but through multiple pathways produce their own beneficial effects that have been shown by functional brain imaging (15). Maybe the non-specific effects being enhanced in certain forms of intervention (e.g. CAM) may explain much of the patient benefit from an intervention (16).

In order to redress the balance more real world "effectiveness" studies are needed, recruiting "all comers" and using more patient-centred outcome measures and global assessments (17). Trials should cover a wide range of age and ethnic groups to take account of adherence and cultural factors.

REFERENCES

1. Herland K et al. *Respir Med* 2006; 99: 11-9.
2. Lazarus SC et al. *Am J Respir Crit Care Med* 2007; 174: 783-90.
3. Bjermer L. *Respir Med* 2006; 100 Suppl A:S17-21. Epub 2006.
4. Travers J et al. *Thorax* 2007; 62: 219-23.
5. Bisgaard H et al. *Lancet* 2006; 367: 286-8.
6. Guilbert TW et al. *N Engl J Med* 2006; 354: 1985-97.
7. Murray CS et al. *Lancet* 2006; 368: 754-62.
8. Everard ML. *J Aerosol Med* 2006; 19: 67-73
9. Ulrik CS et al. *J Asthma* 2006; 43: 701-4.
10. Cai C et al. *Lung* 2007; 185: 105-12.
11. Edwards AM et al. *Clin Exp Allergy* 2001; 31: 1338-40.
12. Stevens MT et al. *Pharm Stat* 2007; (Epub head of print).
13. Barnes N et al. *J Allergy Clin Immunol* 2005; 115: 47-54.
14. Meissner K et al. *BMC Med* 2007; 5: 3.
15. Kong J et al. *J Neurosci* 2006; 26: 381-8.
16. Lewith GT et al. *Evid Based Complement Alternat Med* 2005; 2: 315-9.
17. Marshall S et al. *J Eval Clin PRACT* 2006; 12: 559-68.

RELEVANT COMPETING INTERESTS

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