ABC of Methodology

This is a new Section of *Epidemiologia e Psichiatria Sociale*, that will regularly cover methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

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Explanatory and pragmatic trials

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Randomised trials, that is studies that randomly assign patients to competitive treatments, currently represent the gold standard for evaluating the benefit of pharmacological and non-pharmacological interventions in health care. In the field of pharmaceuticals, randomised trials are typically carried out to establish whether a new treatment is effective in a specific disorder. These trials, conducted for obtaining a marketing authorisation (regulatory purposes), are usually referred as *explanatory* or *phase III* trials.

Explanatory or phase III trials have often been criticised by physicians who are concerned by the fact that, typically, these trials include small samples of highly selected patients that are shortly followed and assessed with sophisticated outcome measures that are rarely employed under ordinary circumstances. In other words, physicians' concern refers to the applicability of results of explanatory trials to typical patients and settings. As a consequence of this concern, in recent years there has been a renewal of interest in *pragmatic* trials (also called practical, effectiveness or management trials, or phase IV studies), that is studies that randomly assign real-world patients to competitive treatments with the aim of assessing their effectiveness under ordinary circumstances (Schwartz & Lellouch, 1967; March *et al.*, 2005; Stroup, 2005; Geddes, 2005).

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Pragmatic trials should not be seen as a research design that should replace explanatory trials. There is a continuum between explanatory and pragmatic trials and, ideally, pragmatic trials should be conducted after the results of explanatory trials allowed a new medicine to enter the market. Clearly, the aim of these two research designs is slightly different: while explanatory trials answer questions about whether an intervention can work under ideal conditions (efficacy), pragmatic trials attempt to answer questions about whether an intervention will work in the real world (effectiveness) (Figure). Recent examples of pragmatic trials include the *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) (Lieberman *et al.*, 2005) and the *Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study* (CUtLASS) (Jones *et al.*, 2006). In Italy a key pragmatic study was an unblinded trial of intravenous streptokinase in early acute myocardial infarction that enrolled 11,806 patients in one hundred and seventy-six coronary care units (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico, 1986).

Explanatory or phase III trials are usually carried out by the pharmaceutical industry, while pragmatic or phase IV trials are more often undertaken by independent physicians. Considering that physicians may require financial support in the conduct of pragmatic trials, specific public health policies have been implemented in different countries. In Italy, for example, in 2004 a Ministerial Decree was issued recognising the public health importance of pragmatic, independent phase IV clinical trials (Tognoni & Franzosi, 2005). In essence, the Decree states that if a set of conditions are met: (a) the study coordinating centre is independent of drug company support; (b) study results can be disseminated

autonomously; (c) there is no personal financial interest in studying the drugs included in the trial; (d) the study drugs are licensed for the indication to be investigated, then the National Health Service (NHS) supports the conduct of the trial in three ways: drug costs are paid by the NHS; there are no fees for submitting the study protocol to the local Ethics Committees; continuing medical education credits are provided to local investigators.

Although the public health importance of pragmatic trials has long been recognised, to date only a limited number of such studies have been undertaken. We argue that physicians should be encouraged to develop skills in the design and conduct of pragmatic trials, and that government support should facilitate their development.

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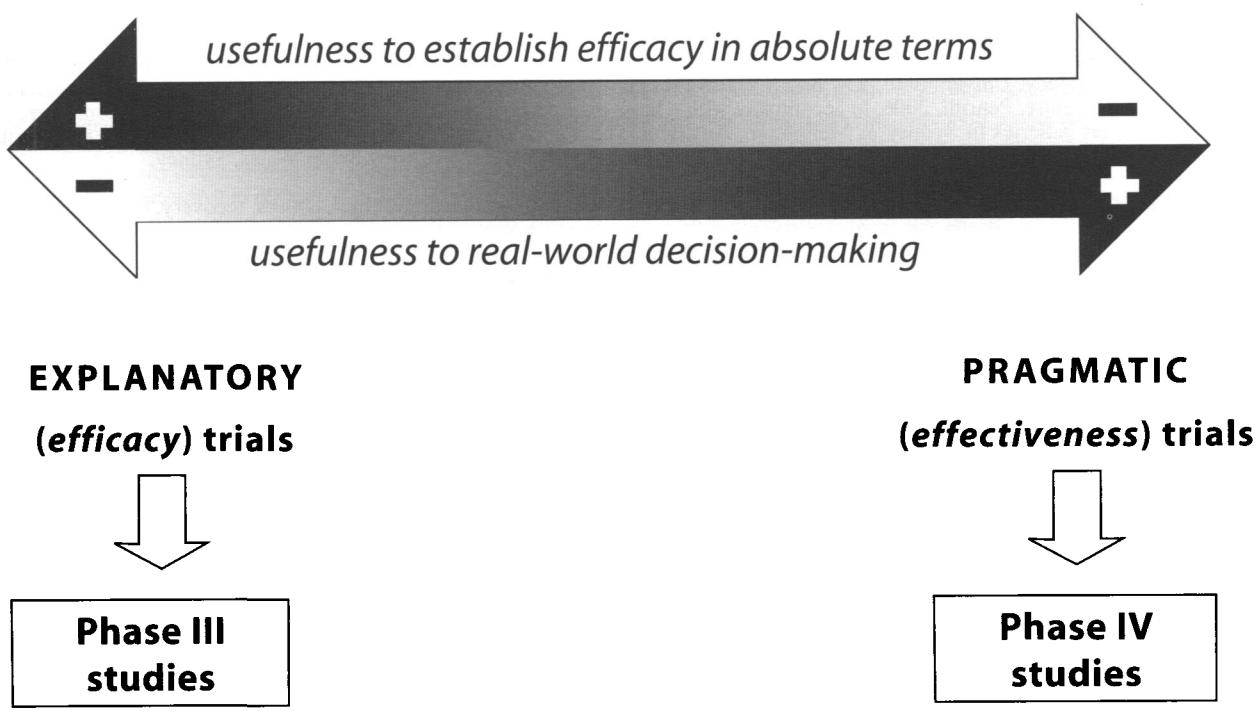

Figure – *Spectrum from explanatory to pragmatic trials.*