Outline



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# A BRIEF HISTORY OF THE RANDOMIZED CONTROLLED TRIAL: From Oranges and Lemons to the Gold Standard

Marcia L. Meldrum PhD *



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The science of medicine in the last 2 centuries has expanded and enhanced the knowledge of the body and of the pathologic conditions which threaten its well-being. The practice of medicine, however, remains an art, because the patient does not always respond to treatment in the way the physician expects. This unpredictability is a greater problem when the treatment itself carries certain risks or deleterious side effects. Even more challenging to simple logic is the converse: sometimes the patient will respond to a *placebo*, a treatment which produces no known physiologic effects at all. To attribute these paradoxes of medical practice to individual variation, whether in genetics or in psychologic conditioning, may be theoretically sound but leaves the problem of constructing "a rational therapeutics" unsolved.[29]

In the twentieth century, to discover the hidden causes of unpredictable and unknown responses to treatment, medical researchers, with the aid of statisticians, have developed a mathematical model to describe and calibrate the complex responses of the human body to therapeutic interventions. The basic principles of this model are (1) comparison, under controlled conditions, of two or more therapeutic regimens (one of which may be a traditional treatment, a placebo, or the exclusion of active treatment), and (2) statistical analysis of the possibility of error. The recognized methodology is the randomized controlled trial (RCT), with its associated features of (1) control groups, (2) randomization, and (3) blinding.

The RCT is by no means a straightforward solution, as even its advocates agree. On the one hand, the principle of comparison often means that one set of subjects will receive a less effective treatment, or possibly none at all, a situation which may sometimes be ethically questionable. On the other, the logistics of designing and carrying out a trial within the real-world constraints of cost, time, and personnel require that the investigators select certain subjects for treatments, specify outcome measures and criteria, and set limits to the duration of treatment and follow-up. These necessary choices and exclusions may affect the statistical result of the RCT or cast doubts on its external validity. As John McKinlay has written,

Recognizing the legitimacy of certain objections, researchers often attempt to accommodate them in the design of an RCT... . In making these accommodations and implementing a study in the real (sometimes hostile) world, certain methodological allowances must be made...the researcher here has been forced by circumstances to depart from the ideal textbook design... . But without these methodological accommodations, the RCT would never have been permitted in the first place. These allowances, which are forced on researchers by practical considerations, are seized upon by critics to discredit the entire RCT... . It is analogous to someone saying they will not attend a party unless they can decide who is to be invited, and then complaining after the party that the company left much to be desired![30]

Nevertheless, the RCT remains the "gold standard." Its power as a model for good practice rests on its imposition of experimental order on the clinical setting and its production of numerical results that may not be absolutely accurate but that are unquestionably precise. As Theodore Porter has argued, the value of the precise quantitative result is that it is readily translated outside its original experimental setting, for replication, comparison, and adaptation elsewhere.[38]

The inferential authority of the RCT has been such that it is accepted as a standard for "rational therapeutics" by physicians and regulatory authorities and also by patients and populations at risk. In the late 1980s, for example, groups such as the Institute for Research on Women's Health documented the exclusion or artificial restriction of women from clinical trials, even when the disease in question affected both sexes, and the scarcity of trial evidence on problems specific to women, such as menopause. In 1991, the National Breast Cancer Coalition challenged the cancer research establishment to carry out trials on new and innovative treatments. In effect, women demanded inclusion in clinical trials and the production of trial evidence specific to their needs.[13, 21] The following decade saw the creation of the National Institutes of Health (NIH) Office for Research on Women's Health and the institution of a number of gender-specific and gender-comparative trials. Today, guidelines for Public Health Service (PHS) grant applications specifically require the inclusion of women unless there is a valid reason for exclusion.

AIDS activists have also demanded RCT expansion, with the Treatment Action Group of ACT UP lobbying for more trials, for the inclusion of more subjects and more minorities, and for the use of active drugs rather than placebo controls. ACT UP proposed the redesign of trial methodologies to make them more sensitive to patient needs, in particular the replacement of life-or-death outcome criteria with surrogate markers of therapeutic efficacy, such as CD4 cell counts. ACT UP's

emphasis on “participatory knowledge making” has been adapted by advocacy groups for Lyme disease, breast cancer, and chronic fatigue syndrome.[7, 8] Although all these groups may criticize trial procedures, they do not reject trial evidence; rather, they seek to participate in its production and to find ways to combine statistical rigor with sensitivity to patient needs. As one activist told sociologist Steve Epstein, “It's about having good science that develops good therapies so that we may have a cure or therapy someday.”[8]

As the clinical trial has evolved in the last 100 years, physicians and scientists—and subjects as well—have faced the same challenge: how to develop “good therapies” based on “good science, ” science that imposes order on, but neither distorts nor devalues, individual human experience. The RCT is a dynamic methodology, and its present and future are informed by its history.

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*Address reprint requests to* Marcia L. Meldrum, PhD, 18311 Lost Knife Circle, #202, Montgomery Village, MD 20886

Pain and Neurosensory Mechanisms Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland

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