

Treatment at Random: The Ultimate Science or the Betrayal of Hippocrates?

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INTRODUCTION

Medicine's principle contract with the patient has for centuries rested on traditional values espoused by the society and the physician: the restoration of health and dignity of the individual through compassionate care. The patient's benefit has been the primary objective of medical intervention. This goal, unambiguously stated in the works of ancient Greek physicians, is explicitly declared in a code of medical practice that over the centuries has come down to us as the Hippocratic Oath.

This simple principle of a beneficent medicine has secured the patient's trust of the physician and has formulated a doctor-patient relationship with which individuals and society at large have been comfortable since antiquity.

In return, society compliments the physician with high esteem. In Homer's world of heroic deeds, "the physician is of the worth of many other men."¹ This relationship has been workable while the principal responsibility of care rests with the physician in a one-to-one exclusive affiliation with the patient.

Corporate health care delivery, as it has evolved in the last century, whether provided by the state or the insurance company, is now challenging this unique relationship and is introducing new concepts of responsibility for the physician that are threatening to undermine medicine's traditional character of beneficence.

In the process of treating individuals, physicians are now required to consider the welfare of the state, of the society, or of the

institution in which they practice. They are now asked to consider the value of life, the cost of life, and the worth of extended life! But how can the restoration of an individual's health leave the society poorer? Why is it now necessary for the physician to declare a commitment to the interests of the society as well as to the individual patient?

A practice that has emerged during the second half of the 20th century and continues unabated at the dawn of the 21st century is that of treatment allocated at random.² This novel approach, often confused with therapy in the minds of physicians and unsuspecting patients, is in essence a research instrument in the service—many believe—of medical progress.

Randomization involves a process by which the treatment to be allocated to an individual is not decided by the physician in charge, but by someone or something else (these days probably by a computer in a remote office that is not necessarily programmed to the individual patient's welfare). This practice has been elevated to the "gold standard" of clinical science.

This gold standard, the randomized trial, is a method of evaluation of the safety and efficacy of a novel treatment or diagnostic procedure in a group of individuals, half of whom will be subjected to the new procedure. The other half may receive a standard or established treatment, no treatment, or a dummy treatment known as a placebo. Who receives what, is a matter of chance.

Why is randomization necessary? Because—it is argued—in this manner, bias in selecting patients with favorable prognostic factors for the treatment under investigation

is eliminated, thus making valid the unbiased assessment of the efficacy of such treatment.

It is believed that the first randomized trial was conducted in Britain in the late 1940s, and the results were published in the *British Medical Journal*.³ The drug under evaluation was streptomycin—the first agent that transformed the natural history of tuberculosis. This trial will be discussed in more detail later.

The substance and concepts of the randomized trial will be considered in this communication from three, often overlapping, perspectives: the philosophical argument for the justification of randomization, the ethical dimension, and the methodology and the magnitude of the question to be addressed.

THE PHILOSOPHICAL ARGUMENT

The advocates of the randomized trial as the gold standard for the evaluation of treatments contend its justification on the principle of uncertainty. Arguably, there are circumstances in which we do not know which way of treating patients is best, and it is necessary to make comparisons to resolve this uncertainty.⁴ This principle has also been referred to as equipoise, and forms the philosophical basis on which random allocation of treatment becomes ethically justified. It means that a clinician or an investigator who may have spent a lifetime in the study of a disease or the development of a treatment is genuinely uncertain about the value of a new drug or method, and is seeking to resolve this uncertainty with a randomized comparison. However, does absolute equipoise genuinely exist in everyday clinical practice?

As Lilford persuasively argues, knowledge, especially clinical knowledge, is not dichotomous.⁵ Knowledge is in a state of constant evolution and information is accrued gradually in what ultimately becomes experience. To categorize this information into absolute known or unknown, thereby ignoring degrees of knowledge (better or less known), is a fictitious dichotomy unrepresentative of the realities of everyday clinical practice.

THE ETHICAL DIMENSION

If we can be persuaded that the dichotomy discussed above genuinely occupies the mind of an individual researcher or clinician, should it affect every other researcher or clinician in the same field of practice?

If I am genuinely uncertain about the value of a new or established treatment, does this also apply to my colleague down the road? My colleague, perhaps with greater experience or different perceptions than my own, may have a greater degree of certainty about the value or otherwise of

the treatment in question. Should then this colleague be obliged to subject his or her patients to randomization to clarify my own uncertainties? Most reasonable people would argue that this is an unreasonable stance, and such differences of certainty are resolved with debate and as evidence evolves with new information.

However, such clinical differences of opinion, the hallmark of intellectual and clinical freedom, are now threatened with erosion. If the state and its appointed agents or institutions (for example, the National Institute of Clinical Excellence in the United Kingdom) resolve that evidence-based medicine emanates primarily, if not exclusively, from randomized controlled studies, my colleague is inevitably subjugated to my own or the state's uncertainties, and may be under pressure to randomize patients.

All of these factors relate to the equipoise of the physician. What of the patient who is enticed to participate in a randomized controlled trial? Is this patient also entitled to equipoise? Lilford provides in his analysis a categorical "yes" to this entitlement.⁵ In addition, if this same patient declines participation in the trial, because for him or her there is no equipoise, should he or she be deprived of all other knowledge preceding the trial?

In the patient's mind, the new (or indeed the old) treatment may look more promising, convenient, appealing, or whatever. Should the patient not have the choice of selecting the new or any other treatment outside the randomized trial? How is such choice possible, however, when the patient is told that the best treatment is not known?

Imagine that you are an acclaimed expert on a particular disease and you are invited to offer your services to your head of state. Will the head of state be enticed to participate in a randomized trial leaving his or her treatment to chance, or will treatment be provided on the best available knowledge of the day? It can be observed safely that there are hardly any prime ministers, secretaries of health, doctors, professors, or similar persons who enlist in the ranks of randomized cohorts that serve the progress of medicine! On what ethical grounds should anyone else become the legionnaire in these randomized cohorts? Imagine now that you are a terrified patient newly diagnosed with cancer hoping for some encouraging news about your treatment from your specialist who is an acknowledged expert on your disease. You soon learn that your expert is not in a position to know!

When during the Medical Research Council's randomized trial of streptomycin, one senior physician contracted tuberculosis, the Medical Research Council obtained supplies for him outside the trial.⁶ In this brief instance of medical history, the equipoise, the ethical arguments, and all other justifications for providing treatment by chance, were thrown out of the window in favor of the human factor—just as they could be when addressing the treatment

of your head of state, your colleague, your old professor, your family, or even yourself.

Pocock and Elbourne⁷ in their discussion of the merits of the randomized trial unreservedly and unequivocally acclaim its experimental design as a powerful quality of the evidence it produces in contrast to the observational study. If this is the case, patients enticed to randomization should clearly be told that they are engaging in an experiment and they are not receiving treatment. Equally, physicians should categorically explain that they are conducting an experiment—they are not administering treatment.

THE METHODOLOGY

Let us assume that all philosophical and ethical arguments have been resolved. In an ideal world, let us assume that researchers and patients enticed to randomization are in genuine equipoise and have no ethical reservations. Indeed, all patients are prepared to participate in the trial because of altruism, for the desire to advance knowledge, because of noble motivation to serve society, and for the benefit of future generations. Will their participation, perhaps their sacrifice, advance knowledge and provide answers that cannot possibly be obtained otherwise? To put it simply, is throwing the dice the only way to obtain the answer? Concato et al⁸ and Benson and Hartz⁹ argue that well-designed observational studies provide valid answers just as efficiently as randomized controlled trials. Others disagree.^{7,10}

It is arguable whether the process of randomly assigning patients always results in the randomization of the disease. The cohorts may be balanced for sex and age, but the subtle variants of the disease, in practice, are hardly ever in equilibrium. If they were, additional evaluation of outcomes with analyses of recognized prognostic factors would be redundant. If the target of a new treatment is the fourth stage of a cancer, will the time interval from the third to the fourth stage of the disease be the same for all patients? This is highly unlikely. If the metastatic sites are in balance in the arms of the cohort, will all patients with liver metastases have the same volume of disease in this organ? This is highly improbable.

It has been argued that randomization will balance known and unknown prognostic factors at baseline.¹¹ On this premise investigators have designed randomized cancer trials in which the only prognostic factors in the cohort that are available for in-depth evaluation of outcomes are the age and sex of the patients. No other crucial prognostic factors are included in the design. However, how many unknown factors can randomization of a cohort of 500 patients accommodate—one, 20, or an infinite number?

Considering these facts, the crucial question remains: is the randomized trial providing evidence that cannot possibly be obtained otherwise? Is the information provided by a

randomized trial of 1,000 patients more reliable than that from 10 observational studies, each enlisting 100 patients? Will the benefits or indeed the toxicity of a treatment investigated in thoroughly reported observational studies remain obscure in comparison with the randomized trial? It can be argued that the quality control of such small studies conducted in specialist units but considered collectively is more reliable than those conducted in the multinational, randomized mega trials. Of course, the immediate reaction to this proposition is that the 10 observational studies will have no control arm, and therefore comparison is not possible.

If the 10 observational studies report response rates between 5% and 20% with acceptable toxicity, the true activity of the new drug or treatment lies somewhere in between. This is what patients and indeed regulatory authorities need to know. How this information relates to past collective experience will determine the place of the treatment in the future. For example, for the vast majority of cancers, any new drug or method that contributes to the control of the disease with acceptable toxicity is likely to find a place in disease management. In these circumstances, both the old and the new treatment become eligible for future use. However, the choice becomes a matter of clinical judgment, which tailors therapy to individual circumstances rather than following blindly the *P* value emanating from the randomized trial.

Could not the same principle apply to the impact on survival? I believe it can. The considerable body of data accumulating on a global scale should be in the service of these objectives. If this was difficult in the second half of the 20th century, it should be feasible with the sudden increase in the use of informatics in the 21st century. If, for example, the European Organisation for Research and Treatment of Cancer boasts cumulative data of disease-specific mega trials enlisting thousands of patients, should this information remain unexploited for future comparisons? It should be exploited, unless of course, the only data reliable from such mega trials merely relate to the age and sex of the recruits.

Proponents of the randomized trial argue that benefits reported from observational studies are not always confirmed with subsequent trials that seek confirmation with randomization. This would be an impregnable argument if all randomized trials always confirmed the results of other preceding randomized trials. This, of course, is not the case.

THE MAGNITUDE OF THE QUESTION

Randomized trials seek to compare treatments, new and old, with a relatively narrow margin of difference, usually on the order of 5% to 10%. A more dramatic effect of a new treatment on a disease, making the benefit palpably apparent, is a rare occurrence even in contemporary therapeutics,

but hardly requires the tribulations of randomization. Whether such small differences enshrined after randomization with statistical validity remain clinically relevant in everyday practice is another matter.¹²

A more critical issue, however, is how firmly the new treatment of small or marginal benefit will entrench in clinical practice. Is there a risk that a favorable but meager comparison will create an intellectual shelter from which only the daring few will exit in the search of new approaches to treatment? If we perceive evidence-based medicine solely as the product of the randomized trial, the risk is real. Others have argued that the fallout of the dogma of the supremacy of the randomized trial stunts the mind, curbs human imagination, and discourages innovative investigators from seeking new approaches to elusive problems.¹³

The practice of medicine is an applied art based on the skills and experience of the physician as well as the evidence of the day. On the other limb of the equation is the patient who seeks the best available care, rather than the best available experiment of the day. In the Hippocratic tradition, the patient's benefit is the focus of clinical practice. The Hippocratic Oath includes two categorical statements that demand the physician's beneficent intervention: "I will apply the regimens of treatment according to my ability and judgment for the benefit of my patients and protect them from harm and injustice," and "Into whatever house I enter, I will do so for the benefit of the sick..." (translation into English by Nicholas Dunkas, MD).¹⁴

The same principles are unambiguously declared in the first treatise of epidemics: "...to help rather than cause no harm."¹⁵ It has been argued that even if the randomized trial were a better investigative method, the ethical imperatives of medical practice over-ride the scientific method, and clinical investigators should urgently explore alternative techniques that avoid the moral burden of randomization.¹⁶ Here the divide comes between the beneficence of the Hippocratic tradition and utilitarianism. If the randomized trial is incited from the belief that a new treatment may be beneficial, by definition and design, one half of the cohort is treated as a utility.

Medicine and the profession have reached a crossroads. Will medicine continue to espouse its traditional beneficent profile or will it adopt the utilitarian approach as it is exemplified by the randomized trial?

At its General Assembly (September 10-14, 2003, Helsinki, Finland) the World Medical Association postponed any decision on proposed revisions to the Declaration of Helsinki.^{17,18} This concerns principally the arguably controversial paragraph 30, which currently stipulates, "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic,

diagnostic and therapeutic methods identified by the study."^{17,18} Nothing seems controversial or ethically ambiguous about this clear, succinct statement that seeks to secure the welfare of the individual while pursuing knowledge and medical progress. Should this paragraph not be retained as it stands in the Declaration of Helsinki?

The alternative takes us to the slippery slope of a ruthless utilitarianism to which medicine and the profession cannot remain indifferent. If ascertaining the truth in clinical science depends more on the precision, objectivity, and integrity of the medical scientist rather than the design of the study,¹² then the randomized trial emerges as a deficient research tool both on deontologic and methodologic grounds. Alternatives are possible and ethically more appealing.

Editor's Note

A commentary follows on pages 5009-5011.

Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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