Was RA Fisher Right?

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Received: 5 August 2016 / Accepted: 11 August 2017 / Published online: 19 August 2017
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Abstract Randomized controlled trials have become the most respected scientific tool to measure the effectiveness of a medical therapy. The design, conduct and analysis of randomized controlled trials were developed by Sir Ronald A. Fisher, a mathematician in Great Britain. Fisher propounded that the process of randomization would equally distribute all the known and even unknown covariates in the two or more comparison groups, so that any difference observed could be ascribed to treatment effect. Today, we observe that in many situations, this prediction of Fisher does not stand true; hence, adaptive randomization schedules have been designed to adjust for major imbalance in important covariates. Present essay unravels some weaknesses inherent in Fisherian concept of randomized controlled trial.

Keywords RA Fisher · Randomization · Adaptive trials

Introduction

A student of biology learns about individual variations in the structure and function of various systems, organs and tissues.

This work has not been presented or published anywhere.

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No two human beings are alike; even identical twins differ in some traits.

No two patients ever show exactly the same constellation of symptoms or signs of a disease. In medical practice, we never encounter a situation, where even two persons present with a tumour with exactly the same size, fixity, grade, shape or similar extent of spread to lymph nodes etc.

Why then Fisher believed that selection of subjects in an experimental trial by process of randomization will distribute all the known factors evenly?

When known factors do not balance, how can we believe that the unknown factors will?

These are some of the questions that a student of “the theory of randomization” enunciated by Sir Ronald A. Fisher may ask. Fisher was working on the fields of Rothamsted Agricultural Station near London, and developed the concept and methods of “randomised controlled trial” in 1925 [1]. He emphasized the need of randomized allocation of intervention in the biological experiments to eliminate the chances of bias in selection of subjects or field plots [2].

The “theory of randomization” states that it would distribute both the known and unknown factors in the two or more groups equally, so that the outcome of intervention may be attributed to the difference in the therapy, unbiased by the variation in the baseline characteristics.

Since all biological creatures including *Homo sapiens* differ among themselves in the most external/outwardly features, it is reasonable to assume, that they would also differ internally or “*Mileu interna* of Claude Bernard”. The differences in the biochemical and genetic configuration and function of vital organs would influence the response of drugs and healing from surgical trauma. Thus, a drug given to one individual

may not have the same effect in another person. We surmise that the fate of a surgical operation in two persons would also be dissimilar. Two persons having undergone the same operation behave in a dissimilar way, depending on their nutritional status, haemoglobin level, immune response, presence of co-morbidity and their psychological status.

Fisher was a highly influential scientist of his time and was instrumental in wide acceptance and adoption of his theory and practice of “randomized controlled trial”. He promoted the method of Fixed randomization.

Today, practitioners of “evidence-based medicine” advocate the use of randomized controlled trial as the only scientifically valid method of deciding about the effectiveness of a therapy, surgery or a preventive strategy.

The conduct of a large number of trials has actually revealed the weakness of Fisher’s theory of equal distribution of known factors in the two or more randomized groups. Hence, authors present their results in “Table 1” of a scientific paper, the “baseline characteristics” in the two groups to show that the randomization distributed, factors equally in the two groups. In other words, “Table 1” of a paper tries to demonstrate that the randomization worked. Sometimes, this distribution is unequal.

Realizing the weakness of “fixed randomization”, newer adaptive methods of recruitment have been developed wherein the investigator can adjust an imbalance in the covariates by continuously adjusting the recruitment. The adaptive methods could either be baseline adaptive or response adaptive [3].

If Fisher was correct in assuming that the magical process of randomization would distribute all human beings similarly in the two groups, the need of adaptive randomization would not have arisen.

Finally, when we witness the failure of randomization in distributing the known (and hence measurable by some gold-standard test) factors, why should we be made to believe that the “hitherto unknown” factors would follow the advice of Sir Ronald. There is no way we could ever measure the unknown factors, because there does not exist a test of measuring them. If there was, the factor would be called a “known” covariate!

Thus, the logic put forth by Sir RA Fisher was not correct and has not stood the test of time. This being so, the statisticians should now begin to question the validity of so many tests that carry the eponym “FISHER”. Time is also ripe for kindling a new paradigm in experimental trials wherein we invent a new method of recruitment of subjects in a study.

The New Paradigm of Allocation

Ever since Abraham Lincoln announced the “Emancipation Proclamation” in 1863, the human beings are trying to liberate their body and soul. We now wish to attain “freedom of speech and work”. We suggest that there should be a “freedom of choice” to get recruited in a particular “intervention arm” of a randomized trial. We should provide detailed printed and pictorial information about the nature of trial, the “state of equipoise” to our participants. Once the subject has understood all aspects of the study, we then should request her/him to choose the desired intervention to arm herself/himself. Besides providing the “freedom to choose therapy”, the trial will also attain greater compliance by subjects, because the selected therapy is close to her/his heart.

The medical community is currently witnessing many restrictions in the conduct of randomized controlled trials. The honorable Supreme Court of India has issued directives to make the consenting of subjects under mandatory video recording of every case. Compensation payment for adverse events or death has necessitated the need of insurance cover for every trial. Our proposed recruitment based on “freedom to choose therapy” would probably avoid these restrictions and the need for heavy compensation.

The authors earnestly seek intellectual inputs to this “emancipation of recruitment” to a randomized controlled trial.

Funding No funding was received for this work.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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