

Study designs in healthcare research

To the Editor

I have read with great interest the recently published article by Arabi¹ in the Saudi Medical Journal and I appreciated the author's efforts and work. Knowing the study designs in biomedical research is very important for any clinician or health researcher irrespective of his major. However, I would like to make few comments on it.

First, the author entitled his review "Study designs in healthcare research" and mentioned later "clinical research" and "medical research". I think that "biomedical research" should replace all of the above due to its comprehensive meaning. Second, I would like to add some to the advantages and disadvantages the author mentioned of the different study designs. In case-control studies prevalence or incidence rates could not be calculated and through such design, we could only estimate the odds ratio and this is considered as one of its disadvantages. Cross-sectional studies are less prone to exposure recall bias and prevalence rates could be estimated through it, as some of its advantages. Of its disadvantages is the antecedent-consequence uncertainty, namely the correct temporal relationship between the risk factor and the disease remain ambiguous in cross sectional studies. The problem of attrition of cohort study participants is one of this design disadvantages. Finally, despite the author mention some advantages and disadvantages of the cross-over and the uncontrolled clinical trials, he did mention nothing on the problems or the ethical debate around placebo-controlled trials versus active-controlled trials, which he referred to as the conventional therapy trials. Unfortunately, the author also reduced the ethical considerations of biomedical research by what he mentioned, "Ethical study is the one that try to answer the scientific question conclusively". The author ignored that the scientific validity of the study, the fair selection of the study participants, the favorable risk-benefit ratio, the independent reviewing process, informed consent, the respect for recruited participants and the study community, collaborative partnership and the social value of the study are the ethical principles of clinical studies.² Of course, placebo-controlled trial is widely regarded as the gold standard for testing treatment efficacy.³ However, such study design has its opponents and defenders. Opponents of placebo controlled trials in conditions for which proven effective treatments exist criticize the use of placebo controls as unethical. They cite the following sentence in the Declaration of Helsinki⁴ as support for their position: "In any medical

study, every patient including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method". The proponents of placebo-controlled trials argue that it would rule out the use of placebo in valuable clinical trials that pose little or no risk of serious harm to human subjects. They also contend that the alternative of active-controlled trials designed to test for the equivalence or "noninferiority" of investigational and standard - or conventional as the author referred to - treatments are subject to methodological weaknesses. They discussed that active controlled equivalence trial lack "internal validity", that is, the efficacy of the investigational agent must be validated by reference to well-controlled data external to the clinical trial. They added that placebo controlled trials are more efficient as they typically require smaller sample sizes to achieve valid results.^{3,5-7} Hence, we could easily notice that placebo controlled trials are caught between 2 orthodoxies, which stimulate other ethicists to endeavor to stake out a middle ground position. Emanuel and Miller⁸ proposed that placebo-controlled trials are permitted but only when the methodological reasons for their use are compelling, a strict ethical evaluation has made it clear that patient who receive placebo will not be subject to serious harm, and provisions have been made to minimize the risk associated with the receipt of placebo.

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"Case Only" design in healthcare research

To the Editor

In an earlier issue of the Saudi Medical Journal, I read with interest the article reported by Dr. Yaseen Arabi entitled "Study designs in healthcare research". Dr Arabi has presented a brief and clear discussion on the research methods usually applied in health care studies with some explanatory examples that are mainly in clinical fields of medicine. I wish to point out that while the paper has almost discussed all the research designs available in healthcare fields, it is missing one new method in this field called "case only" design. The "case only" method was originally designed as a valid approach to analyze and screening of genetic factors in the etiology of multifactorial diseases.^{9,10}

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Some concerns in traditional case-control studies including control group and appropriate selection of control subjects, expensive cost for examining genetic markers in both cases and controls, and time consuming process of such studies have led to the development of this method on studying the gene-environment interaction in human diseases. In a “case only” study, cases with and without the susceptible genotype are compared with each other in terms of the existence of the environmental exposure. Investigators in studying human malignancies have broadly used this method in the recent years. To conduct a “case only” design, the same epidemiological approaches of case selection rules for any case-control study are applied.¹¹ The “case only” study does not, therefore have the complexity of rules for the selection of control subjects which usually appears in traditional case-control studies. The “case only” method also requires fewer cases than the traditional case-control study.¹² Furthermore, for some technical reasons (namely the assumption of independence between exposure and genotype in the population, and so forth), the “case only” design has been studied/ reported to be more efficient, precise and powerful compared with a traditional case-control method.^{13,14} However, there are some important assumptions that must be considered in the application of this model in different studies of genetic factors. More details of these assumptions and assessment of the gene-environment interaction in “case only” studies can be found elsewhere.¹⁵⁻²⁶

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Reply from the Author

I would like to thank the Editor for giving the opportunity to respond to Dr. Afifi's remarks: 1. I understand the personal preference of Dr. Afifi to use the term “biomedical research”. However, Dr. Afifi did not give any reference to support the restriction to use this terminology alone. The terms medical research, clinical research and healthcare research are used to interchangeably in medical literature in the appropriate context including in major journals such as the New England Journal of Medicine, Lancet, Science, JAMA, and British Medical Journal²⁷⁻³⁷ and several standard references.^{36,38} 2. The review article was listed as “short review” and meant to be a concise overview of the subject. As such, and due to space constraint, the article has to be focused on

salient points. It is obvious, however, that any of the study designs mentioned in the article, can by itself a subject of a full review article. Therefore, the points mentioned by Dr. Afifi, were not “ignored” but rather they were not mentioned due to the scope of the article itself. Similarly, the review article was not meant to review the ethics of clinical trials or some of the procedural and regulatory issues in conducting clinical trials. I am pleased to say these issues are being practiced on a daily basis in our Intensive Care Department at King Abdul-Aziz Medical City, as we have been involved in several multicenter international randomized controlled trials. These trials include the randomized controlled trial on the use of non-invasive positive pressure ventilation in post extubation failure³⁹ and the lung open ventilation strategy, which is an ongoing study.⁴⁰ If Dr. Afifi meant to give a comprehensive list of regulatory and ethical issues regarding the conduction of randomized controlled trials, he should also add the requirement for registration of clinical trials.⁴¹ We are pleased that we have 2 internationally registered randomized controlled trials, both are ongoing.^{42,43} and 3. This letter raised an important issue, which is the language of communications in research. Like clinical practice,⁴⁴⁻⁴⁸ the spirit of research should be that of teamwork. As such, constructive remarks are highly welcomed and negative remarks should be avoided. Our successful experience in conducting clinical trials in King Abdul-Aziz Medical City was summarized in an invited review article on teamwork in the field of acute respiratory failure research.⁴⁹ We strongly believe that negative phrases such as the “ignore” should be eliminated from our medical, clinical or healthcare communications.

I thank Dr. Saeed Dastgiri for his remarks.

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