Present Medical Research: Is it Really Original Research Anymore?

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Introduction

I have been a faculty member at several medical institutions in USA for almost 44 years. I am thoroughly disappointed at the quality of present medical research in comparison to research conducted until the turn of the century. I propose the following reasons for the decline in the quality.

Epidemiological studies

Retrospective studies were then shunned by most prestigious and established journals. Presently, a large majority of the articles published in these same journals happen to be conducted by a retrospective design. Unfortunately, almost all these studies are epidemiological in nature demonstrating association between one parameter and another using a statistical analysis establishing 'Relative Risk or Hazard Ratio'. Moreover, most of these studies conduct 'multivariate' analyses and often artificially eliminate multiple variables to satisfy the associations between pre-decided parameters [1]. Finally, RR is almost always statistically significant even with a miniscule ratio (1.1) because of data retrieval in very large populations obtained from registries as well national health and insurance websites via internet and electronic medical records. It must be mentioned that statistical significance often does not translate into clinical significance.

Most frequent design used in these retrospective analyses is to divide a population into tertile or quartile groups based on levels of a metabolite and determination of RR between the metabolite with predecided outcomes. Almost none of these studies document significant correlations between the metabolite and outcomes or attempt to establish pathophysiologic or cause and effect' relationships. The prime example is 'Vitamin D deficiency' and almost all ills in mankind [2]. In fact, vitamin D supplementation has apparently evolved into a big industry despite total lack of

evidence showing remission or even improvement in almost all these disorders following vitamin D supplementation even with megadoses [2]. Association between oral antihyperglycemic agents and cardiovascular morbidity as well as mortality in subjects with type 2 Diabetes without consideration of variability of other important metabolites such as HbA1c, lipid panel and other cardiovascular risk markers using retrospective registry analysis is another prominent example [3-5]. List of similar examples is too large and is beyond the scope of this essay. Unfortunately, this design is being implemented to document increased incidence of a known adverse effects of the drug in comparison to placebo, e.g. greater relative risk of hyponatremia and hypokalemia with a use of diuretic in comparison to other non-diuretic comparators [6]. Sooner than later, a study may appear in the literature showing increased prevalence of hypoglycemia in subjects with diabetes using insulin in comparison to normal subjects administered a placebo.

Meta-analysis

During the last 20 years of the 20th century, medical research funding in USA by private foundations, pharmaceutical companies, major institutions as well as the governmental agencies declined precipitously. Moreover, studies with enrollment of large populations, e.g. over a thousand were not funded by governmental agencies such as National Institute of Health probably because of earlier government sponsored clinical trials such as University Group Diabetes Program creating major controversies [7-9]. Moreover, many long-term population studies such as very well-respected Framingham cardiovascular outcome trial primarily involved Caucasian families [10,11]. Unfortunately, the results of this study are still being applied to subjects belonging to other ethnic groups, e.g. African Americans, Asians, South Americans

etc. As a result, the lack of adequate funding for studying large populations gave way to a new study design of 'meta-analysis' requiring very little or no funding.

Thus, meta-analysis has become 'poor researcher's design to examine data in a large population by involving multiple studies with small populations of subjects. The methodology has become extremely accessible since the advent of internet because of easy retrieval of literature on websites such as 'pub med, medline, google search' etc. Easy access to interested colleagues and a statistician in the department of a major medical institution is primary requisite. Thus, meta analyses are apparently a 'second hand research' a poor substitute for a large population study. Unfortunately, even the pharmaceutical companies are taking advantage of this design by reporting individual clinical trial with enrollment of relatively small populations and reporting a meta-analysis involving the same clinical trials arriving at almost identical conclusions at a later date. For example, many of the individual clinical trials using GLP1 Receptor agonists failed to report increased prevalence of acute pancreatitis and Meta-analysis arrived at the same conclusion obviously because it included the same individual clinical trials [12]. Similar meta analyses have been reported using clinical trials with other drugs as well [13,14]. A major drawback of the meta-analysis is the biases of the researchers regarding inclusion and exclusion criteria for the small studies depending on the similarities of the subjects, the methodologies as well as predetermined outcomes. Hence, the conclusions are frequently questionable and must be critically examined and interpreted. These aforementioned limitations of meta-analysis design are recently very well described [15-17].

Multinational clinical trials

Many major pharmaceuticals have recently embarked upon worldwide multinational clinical trials examining the efficacy as well as safety of their drugs in treatment of chronic disorders, e.g. Diabetes, Hypertension, dyslipidemia on cardiovascular outcomes etc [18]. Apparently, there are several major flaws in the designs of these trials [19-21]. Reporting of the data in the total population irrespective of diversity of ethnicity of the subjects, differences in prominent pathophysiology of disorders in populations with these diversities is a major drawback. Decline in insulin secretion in lean subjects especially of southeast Asian origin in contrast to the rise in insulin resistance in obese Americans with type 2 Diabetes [22-24] or increase in cardiac output and circulating blood volume as a major causative contributor in African Americans in contrast to rising peripheral vascular resistance as a main pathophysiologic factor of hypertension in subjects with other ethnicities are distinctly of importance in the outcomes.

Moreover, variability in prevalence of disorders in populations of different diverse backgrounds is also likely to alter predetermined outcomes. Alternatively, lack of uniformity of methodology because variability of use of medications and goals of therapy for these disorders based on criteria developed by medical organizations of individual nation may be another fraudulent factor. More-

over, the uniformity in the methodology is even further compromised by leaving the choice of the strategy of management of the disorder to the discretion of the individual investigator. Finally, sponsorships and funding of these trials by pharmaceutical companies also raise questions regarding the integrity and reliability of the conclusions since the major incentive for the sponsors is to obtain approval and marketing of drugs in order to generate profits and improve their financial future. Therefore, it is apparent that the data in these trials must be confirmed by additional repetitive results conducted by institutions, agencies or investigators independent of and not connected in any way with pharmaceuticals. Alternatively, the initial trials must be conducted by the same independent entities in order to establish the integrity, purity and reliability of conclusions. Recently, the integrity and reliability of even short-term clinical trials has also been questioned because of the participation by a few same investigators (20%) in development of the design and performance of most (80%) of the trials [25-27]. It is apparent that these few investigators have created 'clinical trial mills' by developing a data base of subjects who hop from one trial to another thus compromising the integrity and reliability. In conclusion, recent medical research appears to utilize inferior designs in terms of methodologies and may also be devoid of highest integrity, accuracy and reliability.

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