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# LETTERS TO EDITOR

## PHARMACOGENOMICS IN CLINICAL TRIALS: AN ANALYSIS

Sir,

Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explore the ways in which these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug or no response at all. Pharmacogenetics refers to the study of inherited differences (variations) in drug metabolism and response. The distinction between the two terms is considered arbitrary, however, and now the two terms are used interchangeably.<sup>[1,2]</sup>

Clinical trials intended to evaluate the safety and efficacy of a new drug in development generally involve large number of patients and are critical to the evaluation and approval of a new drug. The role of pharmacogenetics in clinical trials is to focus on either the further exploration of genetically defined population or the confirmation of pharmacogenetic data from the population to support efficacy and safety of a drug.<sup>[3]</sup> A key component to successful pharmacogenetic research is the collection of samples during the conduct of clinical trials for a drug. Collection of whole blood samples even when no prior hypothesis has been identified may enable pharmacogenetic analysis to be conducted if at any time it appears that there is potential unexpected or unexplained variation in drug response. Since genotypes do not change in an individual, it should be possible to identify

a group that will get clear benefit from the drug by reanalyzing the data from a previously completed trial through genetic stratification.<sup>[4]</sup> The objective of the present study is to analyze the incorporation of pharmacogenetic study in ongoing clinical trials, the type of trials, indications and adequacy of informed consent form.

This was a prospective analysis of the clinical trial protocols with regard to pharmacogenetic component of the study, conducted at the Kasturba Medical College clinical research center, Mangalore. All the ongoing clinical trial protocols were reviewed to check whether any pharmacogenetic study is incorporated. Both blood sample study and tissue sample studies were considered. The informed consent forms were checked for adequacy of information. Of the 50 clinical trials that are ongoing clinical trials, 17 have incorporation of pharmacogenetics with the separately designed consent form. Common indications for pharmacogenomic studies include cancer studies with use of monoclonal antibodies (head and neck cancer, breast cancer, non-Hodgkin's lymphoma), diabetes mellitus, hypertension, sepsis, rheumatoid arthritis, psychiatry disorders, ulcerative colitis, Crohn's disease, atrial fibrillation. Regarding adequacy of information in the informed consent form, all the 17 trials had adequate information incorporated except that there was no information on the fate of sample collected after the specified duration of storage (15-20 years). All patients asked for consent had freely consented. Currently, there is an upward trend in the incorporation of pharmacogenomics in clinical trials. Most of the trials employing pharmacogenomics were on cancer and psychiatry. Blood sample for pharmacogenetic study was usually collected at baseline visit in most of the studies.

Informed consent forms contained sufficient information in all the studies. But none of the consent forms mentioned about the fate of the sample collected once the study is complete. This needs to be clearly mentioned in the consent document. Consent for pharmacogenetic part of the study seems to be freely given, once the subject enrolled in the main study protocol, as there are no direct risks involved. All the patients who took part in the main study participated in the pharmacogenetic part of the study also. It is the responsibility of the investigator to see that the patient has given consent after sufficiently understanding the importance of giving blood sample for pharmacogenetic study.

Pre-screening clinical trial subjects by pharmacogenomics should allow the clinical trials to be smaller, faster and therefore less expensive; therefore, the consumer could benefit in terms of reduced drug costs. Finally, the ability to assess an individual's reaction to a drug before it is prescribed will increase a physician's confidence in prescribing the drug and the patient's confidence in taking the drug, which in turn should encourage the development of new drugs tested in a like manner.<sup>[1,2]</sup> Another potential use of pharmacogenetics is that a drug that has not been shown to be adequately safe and effective in a clinical trial on an entire population may achieve that goal in a genetically defined subset of the population.<sup>[5]</sup> A recent analysis

of adverse drug reactions (ADRs) showed that 59% of drugs causing ADRs are metabolized by polymorphic enzymes as compared to 7-22% of randomly selected drugs.<sup>[4]</sup> This suggests that dose based on individual metabolizing genotype may reduce the risk of ADRs of certain drugs. Similarly, if a breast cancer patient has a tumor that is HER-2 (human epidermal growth factor receptor 2) positive, then trastuzumab (a monoclonal antibody which targets HER-2 receptor) may be an effective therapy. Hence testing for expression of HER-2 in tumor cells is useful in the management of breast cancer.

Pharmacogenomics is one of the fields in which the Food and Drug Administration (FDA) seems to have a large potential to influence the safety and efficacy of drugs by translating the knowledge on this into regulatory actions like drug labels. To provide guidance to the industry, a final 'Guidance for industry: pharmacogenomic data submissions' has been published by FDA. It also offers a new submission path called 'voluntary genomic data submissions' to encourage sponsors that are using pharmacogenomics in exploratory research to submit such information for early discussion with the FDA, but without regulatory implications.<sup>[6]</sup>

Pharmacogenomics can make current and future drugs safer and more effective by targeting them to patients who will benefit the most from them. Only one-third of clinical trials incorporate pharmacogenetics. The combined weight of proven examples whereby pharmacogenetics affects drugs and the possibility of even more examples being elucidated in the coming decades, dictates that pharmacogenetics be incorporated into the drug approval process. Significant effort is also needed to educate different health care professionals about the logistics and benefits of using genetic and genomic information to individualize drug therapy.

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