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REASONS FOR PARTICIPATION AND PROBLEMS ENCOUNTERED BY HEALTHY VOLUNTEERS IN BIOAVAILABILITY / BIOEQUIVALENCE STUDIES

R. Arun Kumar*[1], A. Ruckmani [2], K. Hariharan [3], R. Lakshmipathy Prabhu [4] and A. Priya[4]

Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam – 603103, Tamil Nadu, India

Clinical Research and Experimental Medicine, Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam – 603103, Tamil Nadu, India

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Correspondence to Author:

R. Arun Kumar

Associate Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam– 603103, Tamil Nadu, India

E-mail: arunrmbbs1978@gmail.com

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ABSTRACT: Bioavailability / Bioequivalence (BA/BE) studies are conducted as a part of regulatory requirement to establish that the generic drugs are equivalent to the innovator drugs and are usually carried out in healthy human volunteers. They are nontherapeutic studies without any direct benefit to the participants. In spite of the lack of any direct personal benefit what makes some individuals to volunteer to take part in the study while others are not and what is their opinion about BA/BA studies is largely unknown. Hence the present study was conducted to find out the reasons for participation in BA/BE studies by healthy volunteers and the problems they encountered during the study participation. 112 healthy volunteers participated in this study and all of them were males. From their response, it is evident that 70 volunteers participated in BA/BE studies for monetary benefit. 64 volunteers were of the opinion that free health checkup they undergo in a BA/BE study helps to know their health status and they participated in the studies for this reason. 81 volunteers (72.32%) selected poor toilet facility in CROs as the significant problem. 66 volunteers (58.93%) have expressed that diet restriction was their problem. Inadequate compensation and poor quality of food served during the study were the problems for more than 40 volunteers. For more than 35 volunteers, side effects of the drugs, improper housing facility and frequent blood sampling were the problems during their participation.

INTRODUCTION: New drugs are marketed after extensive research in animals and humans. The research in animals (pre-clinical trials) is carried out to investigate safety, efficacy, pharmacokinetics and toxicity. In humans, clinical trials are conducted in four phases, from phase I to IV to establish whether the new drug is safe and effective for use [1, 2, 3]. These new drugs when marketed are protected with the exclusive patent for certain duration, usually 20 years [4]. When the patent expires, other pharmaceutical companies can manufacture and market the new drugs under generic names without selling them as branded products and these are called generic drugs. This is permitted to create competitive environment in the drug market so that the cost of the drugs reduces and drugs are available to all strata of the community at an affordable price [5].

Generic drugs are approved by regulatory agencies without extensive preclinical and clinical trials as the molecules have already undergone thorough screening conducted by the innovator companies.

However, the pharmaceutical companies have to establish that the generic formulation is equivalent to the innovator (branded) product in terms of efficacy and safety and submit the proof for drug approval [6].

The research study that the pharmaceutical companies are required to conduct in this context to prove equivalence is "Bioequivalence" (BE). It is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study".

One of the commonest methods of establishing bioequivalence for orally administered drug products is by proving the bioavailability of the generic product is not significantly different from the innovator product. Bioavailability is assessed in human beings by administering the drug orally and drawing serial blood samples to quantify the drug in plasma for pharmacokinetic evaluation [7].

It is indirectly assumed if two drug products consisting of the same active pharmaceutical ingredient (API) in the same quantity are having similar bioavailability, their safety and efficacy will also be similar in clinical practice. These comparative pharmacokinetic experiments conducted in human beings to establish bioequivalence are quoted as Bioavailability / Bioequivalence (BA/BE) studies.

Objective of the study: Global harmonization in pharmaceutical business resulted in acceptance of foreign clinical trial data and BA/BE results by different regulatory agencies [8] and multinational pharmaceutical companies started outsourcing their clinical research activities. It created a favorable environment in India for clinical research industry and in the last decade many new Clinical Research Organizations (CROs) came into existence and the number of CROs increased from 60 to 150 [9].

Bioavailability / Bioequivalence (BA/BE) studies are mostly conducted by CROs that have appropriate clinical and analytical facilities and are usually carried out in healthy human volunteers [10], though at times they are done in patients especially for toxic drugs such as anticancer drugs.

In BA/BE studies, there is no therapeutic benefit to the participating subjects, as the studies are mostly done in healthy volunteers. The volunteers are screened for the eligibility, admitted in the clinical facility of CROs and subsequently research study is performed. They are provided with basic amenities for their stay and are compensated for the loss of daily wages and for other study related expenditure. In this process, the healthy volunteers immensely help in the development of low cost generic drugs.

For volunteers, participation in a BA/BE study results in a) absence from their routine work for the period of study duration b) ingestion of drugs which is otherwise not medically indicated c) multiple blood draws and loss of substantial blood volume d) restricted food intake, physical activity e) facing expected and unexpected side effects of the drugs and f) staying away from their houses. In spite of all these sufferings, healthy volunteers participate in BA/BE studies and it is important to understand and analyze the reasons for their participation in BA/BE studies from their perspective, as the reasons could be exploited because of the timeline targets for completing the research projects and profits generated.

Similarly, during the participation in research studies, the volunteers may have inadequacies and discomforts in the infrastructure and study procedures. Evaluation of the problems will help in forming strategies to address them specifically so that the volunteers enjoy being part of BA/BE studies and are further encouraged to actively take part in the studies.

Hence this study was undertaken to find out what the reasons are for healthy volunteers to participate in BA/BE studies and the problems they encounter during their participation.

Methodology: The study was conducted after approval was obtained from the Institutional Ethics Committee of Chettinad Hospital and Research Institute, Kelambakkam, Chennai. It was carried out in a Clinical Research Organization (CRO) in Chennai for the duration of one month and the minimum requirement for the volunteers to participate in the study was that they should have participated in at least one BA/BE study.

Informed consent was obtained from the volunteers who came forward to participate prior to the enrollment. They were not unduly influenced to share their views and they were given a chance to refuse to participate in this study. The details regarding their gender, educational qualification, previous experience in participating BA/BE studies, duration of participation and the number of years of participation were obtained.

They were provided with the evaluation tool to find out the reasons for participation and problems encountered (table 1 and 2 respectively). The list included 5 possible problems, which can be encountered while participating in BA/BE study and 5 probable reasons to participate. The 6th option given was "others" in which the volunteers were encouraged to write any unlisted problem or reason. The volunteers could choose more than one listed item also. The list was designed after discussing with the CRO personnel such as investigator, CRAs and volunteers regarding the reasons and problems. The data collected were tabulated and analyzed.

RESULTS AND ANALYSIS: In this study, 112 healthy volunteers participated and all of them were males. 28 volunteers had education below 12th standard, 28, under graduation and the remaining 56 did not reveal their educational qualification.

81 volunteers opted not to provide information on the duration of participation in BA/BE studies. 15 volunteers had been participating for 1 year and the remaining 16 for 2 to 6 years.

Regarding the number of studies participated, 16 volunteers were part of 5 or less studies. 3 volunteers participated in 6 to 10 studies. Remaining 93 volunteers did not respond.

Reasons to participate: 70 volunteers (62.5%) participated in BA/BE studies for monetary benefit. 64 volunteers (57.14%) were of the opinion that the free health check-up they undergo in a BA/BE study helps to know their health status and they participated in the studies for this reason.

"Less work and relaxation" was the reason for participating in BA/BE studies for 41 volunteers (36.61%). 39 volunteers (34.82%) have chosen "help marketing new and cheap drugs" and 33 volunteers (29.46%) considered it a social service too.

The response of the volunteers for the query on reasons to participate in BA/BE studies is given in **table 1 and figure 1**.

TABLE 1 – REASONS TO PARTICIPATE IN BA/BE STUDIES

Reasons to participate	Yes		No	
	N	%	N	%
R1 Earn extra money	70	62.50	42	37.50
R2 Free health check-up and know health status	64	57.14	48	42.86
R3 Help marketing new & cheap drugs	39	34.82	73	65.18
R4 Less work and relaxation	41	36.61	71	63.39
R5 Social service	33	29.46	79	70.54
R6 Others	-	-	-	-

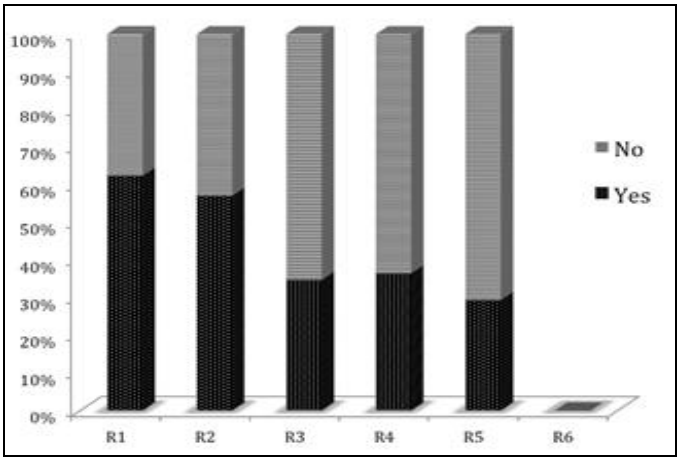

FIG. 1: REASONS TO PARTICIPATE IN BA/BE STUDIES

Problems encountered: Poor toilet facility in the CROs was found as the problem by 81 volunteers (72.32%) during their participation in BA/BE studies. 66 volunteers (58.93%) were of the opinion that diet restriction in a BA/BE study is the problem.

43 and 45 volunteers selected inadequate compensation and poor quality of food served respectively. More than 35 volunteers have expressed that side effects of the drugs, improper housing facility and frequent blood sampling were the problems during their participation.

19 volunteers did not like bunker beds used in CROs and more than 20 volunteers have felt that compensation amount has not been paid on time and the amount paid was also not as stated prior to the study participation. 21 volunteers have chosen physical activity restrictions imposed during the stay in CROs.

The response of the volunteers for the query on problems they encountered while participating in BA/BE studies is given in **table 2 and figure 2**.

TABLE 2: PROBLEMS ENCOUNTERED WHILE PARTICIPATING IN BA/BE STUDIES

Problems encountered	Yes		No	
	N	%	N	%
P1 Side effects of the drugs	35	31.25	77	68.75
P2 Quality of food	45	40.18	67	59.82
P3 Improper housing facility such as				
P3i Inadequate area	38	33.93	74	66.07
P3ii Bunker beds	19	16.96	93	83.03
P3iii Poor toilet facility	81	72.32	31	27.67
P4 Compensation				
P4i Inadequate	43	38.39	69	61.61
P4ii Not paid as stated	27	24.11	85	75.89
P4iii Time delay in getting it	22	19.64	90	80.35
P5 Study procedures such as				
P5i Diet restrictions	66	58.93	46	41.07
P5ii Physical activity restrictions	21	18.75	91	81.25
P5iii Frequent blood sampling	39	34.82	73	65.18
P6 Others	-	-	-	-

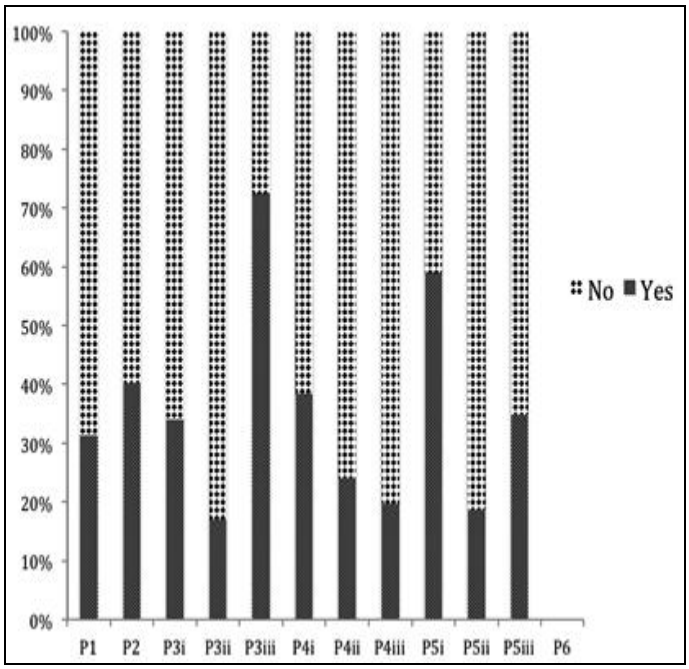

FIGURE 2: PROBLEMS ENCOUNTERED WHILE PARTICIPATING IN BA/BE STUDIES

DISCUSSION: All the volunteers participated in the study were males. Though the guidelines recommend that BA/BE studies shall be conducted in both males and females[11, 12], during the study period, no female volunteer was participating in the studies carried out in the CRO where this survey was conducted.

It indicates that females participate less in BA/BE studies compared to males. The reason could be that participation in BA/BE studies requires them to stay in the clinical facility of the CRO till the study is completed. Because of the socio cultural practices of the Indian society, females are not encouraged to stay away from their houses normally.

In this study, 62.5% of volunteers have opined that they have been participating in BA/BE studies for monetary benefit. It is fairly understandable from volunteers' point of view that they put in their efforts and withstand study discomforts mainly for monetary compensation since BA/BE studies are non-therapeutic in nature. The CROs can compensate the volunteers to the extent of reimbursing the loss of wages, transportation and incidental expenses according to guidelines whereas the compensation cannot be huge to influence them to participate in research studies [13, 14].

Ethical guidelines published by Indian Council of Medical Research states that the compensation cannot unduly induce people to participate in research activities and the ethics committees should approve compensation packages proposed for study participation [13].

The same is reiterated by Indian Good Clinical Practice (GCP) guidelines [14], but there is no mention about the compensation for participation in research in schedule Y of drugs and cosmetics act [15], though it mentions compensation for research related injuries. The Indian BA/BE guidelines published by CDSCO in 2006 also did not mention about volunteer compensation for participating in BA/BE studies[16]. The rules and guidelines generally recommend the volunteers could be compensated for research participation, but there is no methodology recommended for fixing the compensation in BA/BE studies and it could become a reason for exploitation, as the volunteers may be lured towards the studies by offering undue and high monetary package.

More than 40% of the volunteers feel that the compensation provided is not adequate and quality of food is not good. Over 20% of them have opined that they did not get the entire compensation, which was promised prior to participation, and there was a delay in paying the compensation also. The volunteers should be encouraged to inform such malpractices to the ethics committees and ethics committees also should actively involve in identifying, and preventing them. Proactive functioning of the ethics committee will improve the standard of CRO practices in this regard.

CROs maintain clinical facilities to house the volunteers for conducting BA/BE studies. The clinical units are located in controlled environment that includes defined areas for beds, toilets, recreation, dining and other study activities. The areas are designed to provide comfortable stay to the volunteers as well as help conducting the studies. To accommodate more volunteers in a limited space, CROs might adopt a practice of keeping bunker beds and it might throw a safety concern while the study is conducted. If the drug has the potential of causing cardiovascular or neurological side effects such as hypotension, giddiness, convulsions and fainting, the volunteers in the upper bed may fall down and get injured.

Moreover, in any medical emergency, resuscitation of the volunteer in the upper bed will be difficult and crucial initial time will be spent in accessing the volunteer and not in resuscitation. However, only 16.96% of volunteers have stated bunker beds are problematic.

The volunteers should be housed in clean hygienic environments during the study, otherwise it will pre-dispose to infections and subsequent health related complications. It is surprising that 81 volunteers out of 112 were of the opinion that toilets are poorly maintained in CROs. It could be due to either less number of toilets, poor maintenance or both and the CROs should ensure the adequacy and cleanliness of the toilets. A healthy volunteer participating in a BA/BE study should not become sick due to the unhealthy environment.

There are discomforts in every BA/BE study in the form of study procedures such as frequent blood sampling, food restriction and physical activity restrictions. Blood samples are collected to assess the drug concentration and pharmacokinetics. The volunteers have to be educated properly about the objectives of BA/BE studies and blood sampling. They need to be aware of the reasons for food and physical activity restrictions so that they fully cooperate for the restrictions. Though the procedural details are informed during the consent process, 58.93% of the volunteers have selected food restriction, 34.82%, frequent blood sampling and 18.75%, physical activity restriction as significant problems.

The monitoring authorities such as ethics committees and regulatory agencies should make periodical inspections of CROs and get view of the participating volunteers. This will assure the volunteers' rights, safety and wellbeing while they participate in clinical research.

CONCLUSION: It is evident from this study that the volunteers participate in BA/BE studies mainly for the monetary benefit and poor toilets are their significant problem while they participate in the studies. Currently there is no guideline for calculation of compensation for participating in BA/BE studies. It will be better if the regulatory agencies frame policies as otherwise it could be a factor for exploitation. Similarly, the agencies and ethics committees should take proactive role in implementing basic housing requirements such as clean toilets, proper beds and environment and quality food. It has to be emphasized that the volunteers participating in the BA/BE study must enjoy the basic and affordable comforts without any compromise on the ethics, safety and study requirements.

DECLARATION: The project was the original work carried out by the authors in a CRO and its name is withheld for confidentiality as per the terms of agreement with the CRO. This was not funded and the authors personally met the expenses.

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