SPECIAL ISSUES IN CLINICAL RESEARCH: CONFLICT OF INTEREST, POST TRIAL DRUG ACCESS AND USE OF PLACEBO IN CLINICAL TRIALS

Article Review by Maduri Patel, Kannan Sridharan, Jayesh Patel, Shraddha Ghai, India
(PhD in Clinical Research, Texila American University)
Email: - madhuri_zeal_112@yahoo.com

ABSTRACT

The aim of this study is to identify ethical issues and challenges in clinical research in India. This study provides clear picture of special ethical issues in clinical research such as conflict of interest, post trial access to investigational product and use of placebo. We examined clinical research professional perceptions on those issues.

Individuals (N=385) working in field of clinical research in India have participated in the study. This study involves self administered survey research for collection of data and information from participants through their responses. The survey questionnaire was validated by colleagues and guides and experts in the field. The survey elicited responses based on general experience and opinions of clinical research professionals. Participants were given the option to complete the survey on the internet. Surveys completed via the internet were stored in Microsoft excel. For data analysis SPSS software have been used and descriptive analysis have been conducted.

A total of 389 surveys were received, of which 385 were considered complete and used for this analysis. The respondents were from India, currently working in clinical research field. Demographic information pertaining to respondents such as education, type of organization age, experience etc have been collected, whether they had ethics training ever, and if yes which type of training they had. The data shows that majority have responded that they are not favouring post trial access to investigational product or it is not ethical. Further to that, participants were asked to select reasons for their opinion on post trial access to investigational product. If participant believes that post trial access to investigational drug is ethical, they have selected applicable reasons for their opinion. Majority of respondents favour use of placebo in clinical trials in general. If participant is favouring the use of placebo, further they have provided their opinion on possible steps to be taken care of in placebo controlled trial. Participants has been asked to rate the factors which can promote or causes conflict of interests in clinical trials. As per data, financial gain is the most affecting factor causing conflict of interests. Comparing

responses employer wise, CROs, ECs and Study sites are rating "recruitment target" more than sponsors. The data shows that industry influence, patent or other commercial benefits are not highly affecting.

KEY WORDS

Placebo, Conflict of interest, post trial access, ethics

INTRODUCTION

Clinical research is well defined and organized research conducted oh human beings, to provide information on drug's safety and efficacy. There are international and national recognised clinical research guidelines that form the basis for conduct of ethical clinical trials. Many human research codes and guidelines have developed over the past century such as the Declaration of Helsinki, Nuremberg Code- a set of ethical principles for research on human being. These ethical principles formulated after discovery of inhumane behaviour with humans. Ethics in clinical research largely focuses on acceptable conditions for exposure of clinical trial participants to burden and risk for the benefit of society. The focus of ethical clinical trial has been on protocol review, monitoring of subject safety and welfare, study design, informed consent etc. this article describe the special issues arises in conduct of clinical trial i.e. post-trial access of investigation product, use of placebo in clinical trials and conflict of interests.

Investigators are failing to disclose financial ties, considerable payments, gifts to physician. To prevent the situation every entity involved in clinical trials should take initiative to adopt stringer policies. Hundreds of journals publish innumerable research paper, and based on these literature clinical guidelines are prepared. Thus biomedical research also feeds the judicious use of current best evidence for treatment and patient care decision.[1] Conflict of interest is a condition and therefore circumstances determine presence of conflict of interest.[2]

Post-trial access (PTA) to investigational product has been a matter of discussion since late 1980s, linked with trial carried out for acquired immunodeficiency syndrome in developing country. However, the complexity of the issues is not ways to address and required specific discussion. This concern is certainly in developing countries due to poverty, illiteracy, limited resources, insufficient access to healthcare services and lack of familiarity with clinical research.[3] Post-trial access to study drug is merely not ethical issue but also includes legal and policy issues and disputes.

METHODOLOGY

The study involved a self administered survey and was approved by the Texila American University Advisory Committee. It consisted of 35 questions, covering informed consent, ethics committee reviews, post trial access of investigational product, financial and non conflict of interests, regulatory rules and guidelines, ethical codes and principles, use of placebo,

misconducts, documentations, clinical researchers' recommendations. The survey questionnaire was peer reviewed by colleagues and guides and experts in the field. The survey elicited responses based on general experience and opinions of clinical research professionals. Questions related to conflict of interests, post trial access and conflict of interests will be reported in this paper. The study has no source of external funding and funded by the author. Snowball sampling method was used for data collection as respondents are difficult to locate. Few clinical researchers have been located and contacted via email and/or telephone, and invited to participate in the survey. Then asked those participants to provide information needed to locate other individuals who were eligible to participate in the survey. Invitation to participate in survey was assumed to have reached 380 participants. Participants were given the option to complete the survey on the internet. Data collection took place over five months. No incentive was given to participants. Surveys completed via the internet were stored in Microsoft excel. Survey in which minimum 10 % of questions were answered was considered "complete" and was used for data analysis. This database was used to determine frequency of responses by each variable and multivariate analysis to evaluate correlation of two or more variables. To measure the strength of association between variables, tests of significance, such as x2 test and respective p values, were calculated.

RESULT

A total of 389 surveys were received, of which 385 were considered complete and used for this analysis. The survey was designed such that there were skip patterns for some questions; therefore the number of responses (n) varies for different questions. The respondents were from India, currently working in clinical research field. Demographic information pertaining to respondents is shown in figure number 1 to 3 (age, Education, type of organization) Figure 1 shows, 169/385 (43.9%) of participants are 36 to 45 years of age followed by 21 to 35 Years 142/385 (36.9%) and 46 to 60 years 74/853(19.2 %). Type of organization where participants are working or belong to is shown in figure 3. Out of 385 participants, 181/385 (47 %) are working with site and 162/385 (42.1%) are associated or working with CROs. 19/385 (4.9 %) of participants are working in EC and 19/385 (4.9 %) with sponsor companies. These data shows that most of the research activities must be taken care by CROs and research sites. As per current practice, most of the sponsors are out sourcing research activities to CROs, so it is obvious that much less people from sponsors' end are involved in clinical trials.

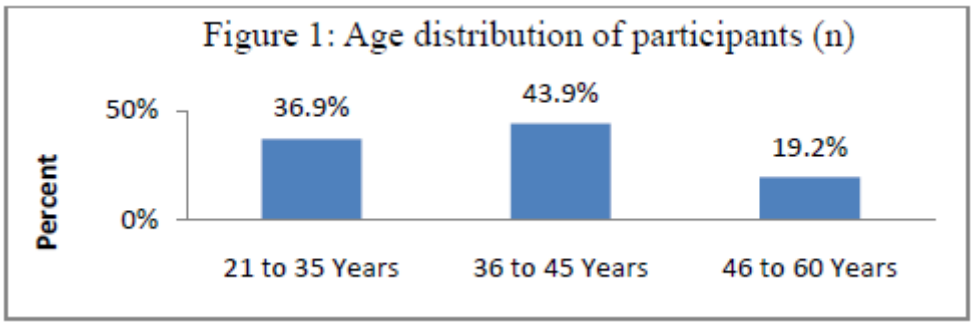
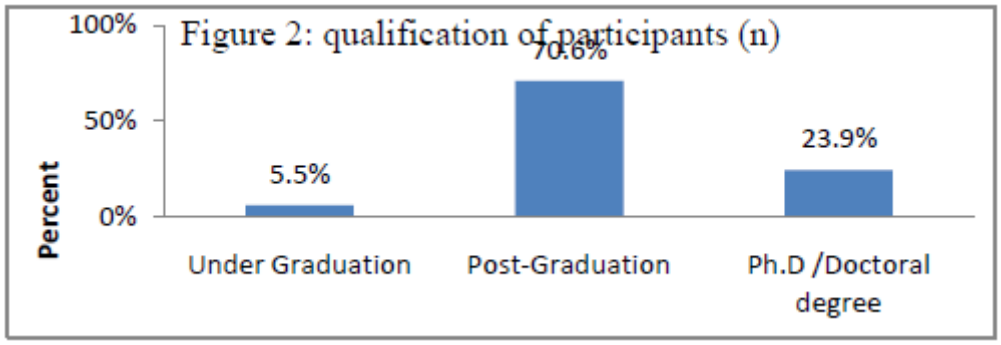


Table 1 shows the number of years working experience of participants in clinical research. The data shows that 146/385 (37.9%) participants have 11 to 15 years of experience in field of clinical research, while only 10/385 (2.6 %) are having less than 2 years of experience. 236/385 (61 %) of sample had more than 10 years of research experience.



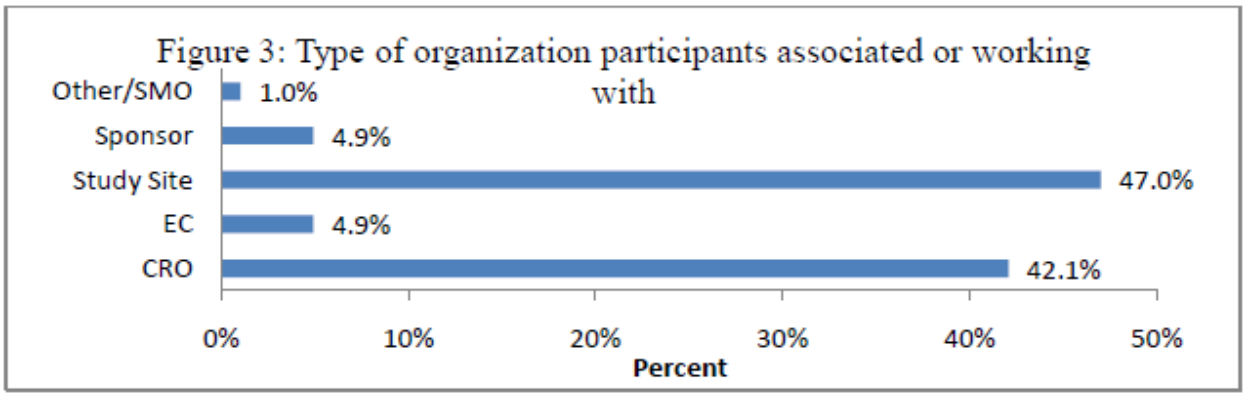


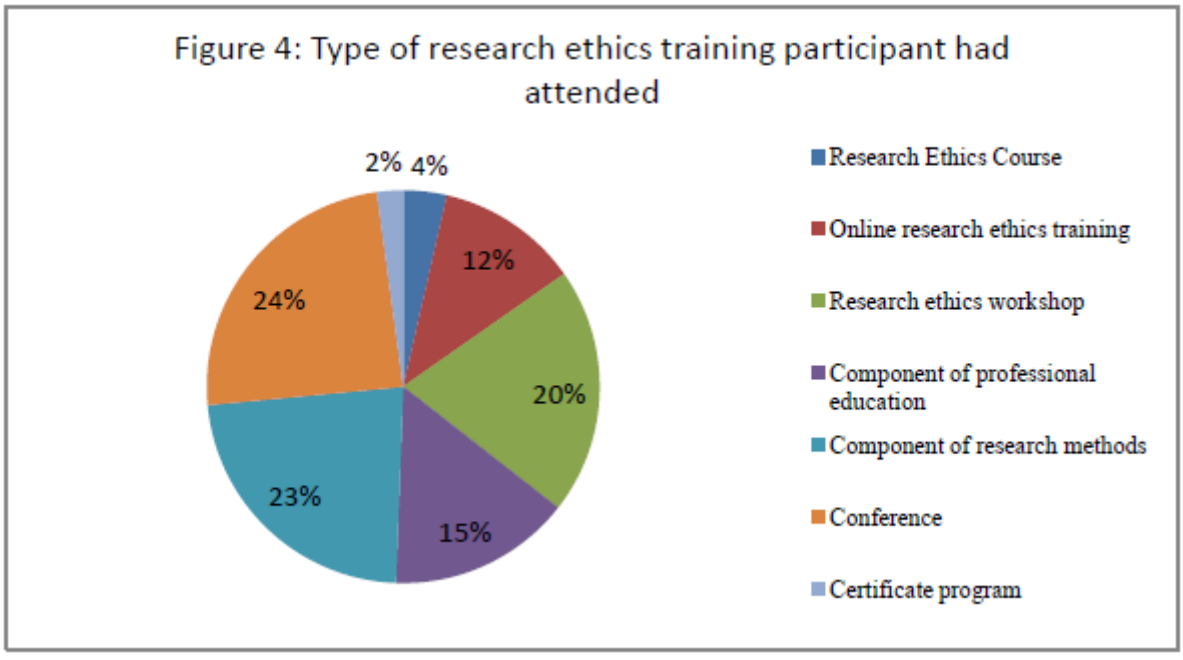
Table 1: Number of years working experience in Clinical Research

How long have you been working in field of Clinical research?	**Count**
Less than 2 years	10 (2.6%)
3-5 years	39 (10.1%)
6-10 years	100 (26.0%)
11-15 years	146 (37.9%)
16-20 years	74 (19.2%)
More than 20 years	16 (4.2%)
Total	385 (100.0%)

In the questionnaire, participants are asked whether they ever had formal research ethics training. Table 2 shows 233/385 (60.5%) of participants have responded that they had formal research ethics training while 152/385 (39.5%) had never attended formal ethics training during their carrier. Further to that, participants are asked which type of research ethics training they have attended if they have answered yes. It is also possible that few participants have attended more than one type of training. Figure 4 shows the type of ethics training participants have attended. Our data suggests that we need to develop research ethics program and courses. Online program can be more useful as more professionals can be benefited and international standards of ethics can be developed.

Table 2: Formal research ethics training

Have you ever had formal research ethics training?	**Count**
Yes	233 (60.5%)
No	152 (39.5%)
Total	385 (100.0%)



Our data shows that only 101/356 (28.4%) of respondents have ever served in EC, and 255/356 (71.6%) have never served in EC.

Table 3: Post trial access to investigational product

Should post-trial access to investigational drug is ethical?	**CRO**	**EC**	**Study Site**	**Sponsor**	**Other/SMO**
Total	162 (100.0%)	19 (100.0%)	180 (100.0%)	19 (100.0%)	4 (100.0%)
Yes	24 (14.8%)	7 (36.8%)	59 (32.8%)	6 (31.6%)	3 (75.0%)
No	138 (85.2%)	12 (63.2%)	121 (67.2%)	13 (68.4%)	1 (25.0%)

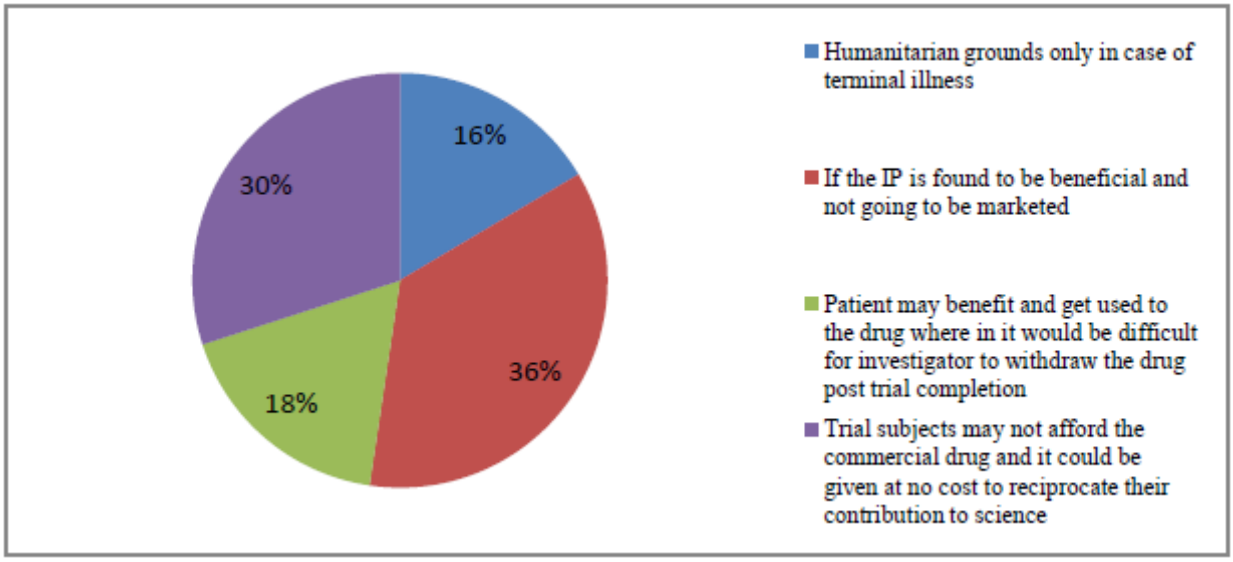


Figure 5: Reasons if participant favouring post trial access to investigational product

During the survey, participants have been asked whether they support post trial access to investigational product to subjects. The data shows that majority have responded that they are not favouring post trial access to investigational product or it is not ethical. Table no. 3 shows the summary of their responses. Participants from CROs 138/162 (85.2%) believe that post trial access to investigational drug is not ethical and 3/4 (75 %) from other organizations or SMOs believe that it is not ethical. 13/19 (68.4 %) participants working with Sponsor believe that it is not ethical. When looking at responses from study site and EC members respectively 59/180 (32.8%) and 7/19 (36.8%) participants believe that it is ethical.

Further to that, participants were asked to select reasons for their opinion on post trial access to investigational product. If participant believes that post trial access to investigational drug is ethical, they have selected applicable reasons for their opinion. Figure 5 shows that 36% of participants have selected “If the IP is found to be beneficial and not going to be marketed” and

30% of participants have selected "Trial subjects may not afford the commercial drug and it could be given at no cost to reciprocate their contribution to science". 18 % believes that "Patient may benefit and get used to the drug where in it would be difficult for investigator to withdraw the drug post trial completion", while 16 % have selected "Humanitarian grounds only in case of terminal illness". Figure 6 shows the reasons if participants do not favour post trial access to investigational product. 48% participants have selected "post end of study could change the efficacy/safety information to preclude such treatment".

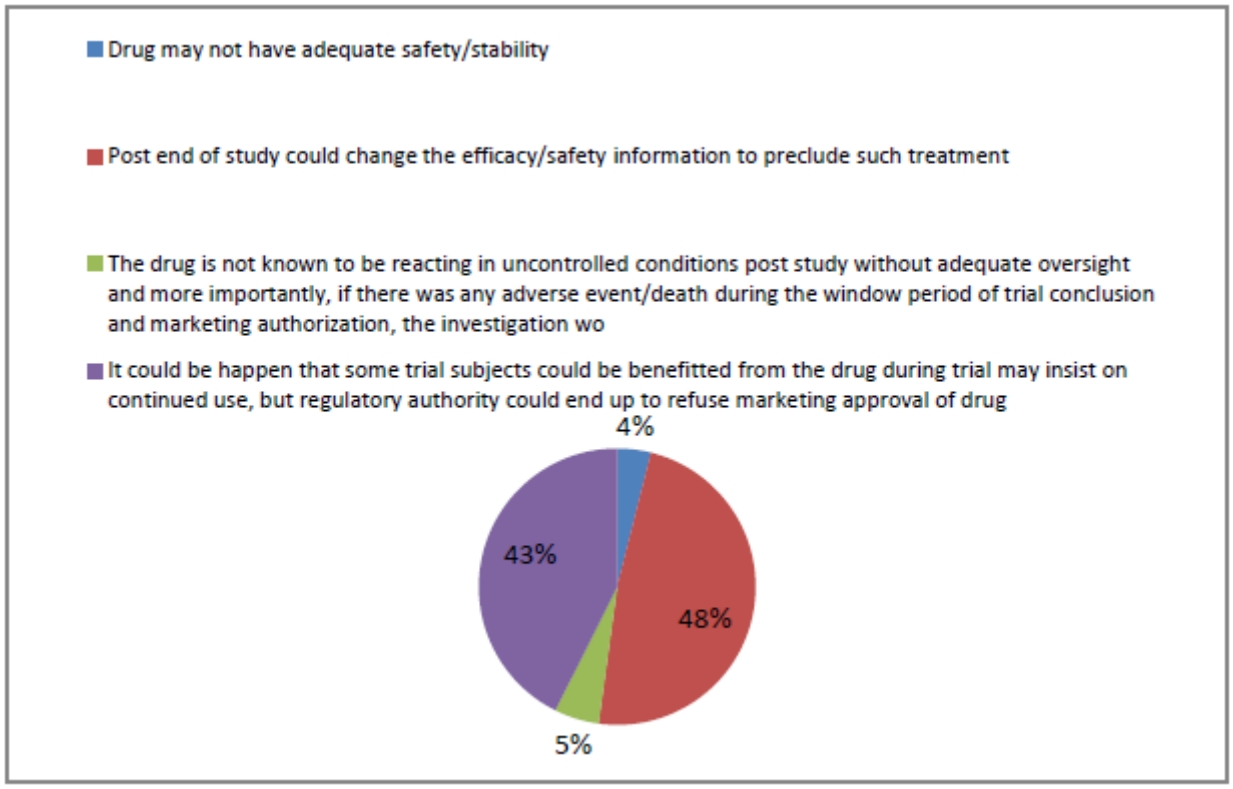


Figure 6: Reasons if participant not favouring post trial access to investigational product

Table 4: Use of placebo in clinical trial

Do you favour use of placebo in clinical trial in general?	**CRO**	**EC**	**Study Site**	**Sponsor**	**Other/SMO**
Total	150 (100.0%)	18 (100.0%)	178 (100.0%)	19 (100.0%)	4 (100.0%)
Yes	145 (96.7%)	16 (88.9%)	168 (94.4%)	18 (94.7%)	3 (75.0%)
No	5 (3.3%)	2 (11.1%)	10 (5.6%)	1 (5.3%)	1 (25.0%)

Whether participants favour use of placebo in clinical trials is shown in Table 4. Majority of respondents favour use of placebo in clinical trials in general. If participant is favouring the use of placebo, further they have provided their opinion on possible steps to be taken care of in placebo controlled trial, as shown in Table 5, where group analysis is presented.

Table 5: Justifications in which situation Placebo should be used

	CRO	**EC**	**Study Site**	**Sponsor**	**Other/SMO**
Total	145 (100.0%)	16 (100.0%)	165 (100.0%)	18 (100.0%)	3 (100.0%)
The said disease had no defined/established standard of care	96 (66.2%)	6 (37.5%)	62 (37.6%)	6 (33.3%)	1 (33.3%)
Adequate rescue procedures for patient withdrawal and safety management ensured	68 (46.9%)	8 (50.0%)	99 (60.0%)	10 (55.6%)	0 (0%)
Back-up investigators present at the site for additional oversight	26 (17.9%)	5 (31.3%)	47 (28.5%)	4 (22.2%)	2 (66.7%)
Additional monitoring ensured by the sponsor/CRO	77 (53.1%)	9 (56.3%)	70 (42.4%)	11 (61.1%)	2 (66.7%)

Standard treatment should also be available with placebo	34 (23.4%)	4 (25.0%)	28 (17.0%)	4 (22.2%)	0 (0%)

Table 6: Conflict of interest

Rate the following areas of conflict of interest in clinical trial according to their existence. (1 is minimum, 10 is maximum)	**Median**				
	CRO (1-10)	**EC (1-10)**	**Study Site (1-10)**	**Sponsor (1-10)**	**Other/SMO (1-10)**
Academic (Desire for prestige, power, faculty advancement, interest in obtaining positive results, pressure/desire to publish, recruitment target)	4.0 (1-7)	4.0 (3-7)	4.0 (2-9)	5.0 (2-10)	4.5 (1-7)
Institutional conflict of interest	5.0 (1-8)	5.0 (4-7)	5.0 (1-9)	5.0 (2-8)	6.5 (2-8)
Personal (Preference for family and friend, desire to alleviate human pain and suffering	3.0	3.0	3.0	5.0	4.5
Compromise in appointment or promotion	3.0 (1-9)	3.0 (1-6)	3.0 (1-8)	3.0 (2-10)	4.0 (1-4)
Its relative weight in professional decisions on meeting recruitment targets may pose problem	7.0 (1-9)	7.0 (3-8)	7.0 (1-9)	3.0 (1-7)	5.5 (1-6)
Industry influence, patent or other commercial etc	1.0 (1-9)	2.0 (1-9)	2.0 (1-10)	3.0 (1-8)	7.0 (5-9)

Financial gain	8.0 (1-10)	8.0 (2-10)	8.0 (1-10)	8.0 (4-9)	7.0 (4-10)
Ignorance in AE reporting because it can be responsible for licensing	5.0 (1-10)	5.0 (1-6)	5.0 (1-10)	5.0 (2-10)	7.0 (4-8)
Favouring pharmaceutical company/EC/Sponsor/CRO/Investigator/Regulatory	1.0 (1-8)	2.0 (1-8)	2.0 (1-8)	2.0 (1-10)	4.0 (2-9)

During the survey, participants has been asked to rate the factors which can promote or causes conflict of interests in clinical trials. Table 6 shows the summary of responses. As per data, financial gain is the most affecting factor causing conflict of interests. Comparing responses employer wise, CROs, ECs and Study sites are rating "recruitment target" more than sponsors. This topic should be studied more because the data shows there might be gap between perceptions of sponsors and other clinical research professionals about recruitment target. It could be happen because sponsor wants to recruit patients as soon as possible, but they might ignore the fact that it can cause conflict of interests. The other factors causing conflict of interest such as academic desire, institutional conflict of interests, personal, ignorance in reporting adverse events, compromise in appointments, favouring other stakeholders are also shown in table 6. The data shows that industry influence, patent or other commercial benefits are not highly affecting but SMOs/others rated it little high. It could be because very few numbers of participants are from that type of organization. However, we cannot ignore the value, and further research is required for the same. Table 6 gives more detail about the rating for other factors.

DISCUSSION

This study reflects the expressed opinions and attitudes of a sample of clinical research professionals from India and has provided an insight into ethical issues in poor setting. To our knowledge this is the first study of this nature with empirical data from Indian respondents. Over the past few years, pharmaceutical companies have shifted trials to developing countries like India because it is easier, cheaper and oversight is minimal. However, regulatory has not expressed a stand on manner in which the industry is growing in India.

Conflict of interest is "a set of conditions in which professional judgement concerning primary interest such as research, education or patient care tends to be biased or influenced by secondary interest such as financial gain or personal prestige".[2]

Sometimes, investigators recruit patients for experiments where patient are even not well informed about the study whether the study is funded by government and investigators have n possibility of financial gain from it. In such cases, the primary motive is academic that desire to gain knowledge. And the secondary motive is to advance career by publishing the result of research and to get grant support, academic currency that buys prestige and promotion. Several studies have shown the financial conflict of interest make doctors to refer patients for particular medication, test, operation or procedure.[4, 5] Conflict of interest have effect on publication too. Sometimes it happens that papers published in journal supplements sponsored by pharmaceutical companies are poor to those in parent journal.[6]

There may even be a conflict where a person is working as a research and physician at the same time, Where investigator have additional interests that may not be relative to their patient's interest.[7] A secondary interest could be altruistic for example the continued employment of the researcher. A typical example of conflict of interest related to personal gain is physician self-referral. As described in about definition of conflict of interest, the reference to "set of conditions" is important; having a conflict of interest is an objective situation and does not depend on underlying motives. The potential for conflict of interest on the part of the investigator is widely expressed concern. Conflict of interest can lead to bias in design, conduct, analysis, reporting and interpretation and communication of result. Thus, the conflict of interest is generally considered in the financial, but other conflicts such as intellectual may also occur.[8] Ideally, no investigator would have any interests other than the well-being of the study participants and the generation of new knowledge that will improve clinical care and public health. That is unrealistic, however, given that most investigators receive research funding from government, industry, or others with considerable interest in the outcome of the study.

During past two decades, increasing attention has been paid to financial conflict in clinical research because of relationship between investigators and industry. This relationship causes conflicts in conducting, interpreting and reporting of research. The death in 1999 of subject enrolled in study in which investigator and sponsor had financial interests accelerated efforts to raised concerns for financial conflict of interests.[9] However, the death of other research subject is not only because of financial conflict. Sometimes, the problem include the excessive zeal of an investigator to complete the study, an inadequate literature review on toxicity, the potential vulnerable patients to serve as subject, failure to report adverse events to ethics committees, use of poorly trained personnel to measure dose etc.[10] Deaths and injuries are rare even in research involving volunteers who have no underlying diseases. There is no reason to believe that it occurs in studies in which financial conflict is existing.

The first step in managing financial conflict of interest is for the leader to acknowledge that these conflicts are basic to research, whether or not there is financial conflict of interest. Each institute must promote expectation that each person involved in research will act with that conflict firmly in mind. Institutional policies should address both the financial and nonfinancial conflict of interests. The institutional emphasis on this category of conflict of interest wills ethics

committees in their difficult task of balancing the value of research and safety of patients. The EC members themselves subject to the influence f a nonfinancial conflict of interest as majority of them are researcher, employees and colleagues of investigators. The National Bioethics Advisory Commission has recommended that persons who represent the perspectives of subjects, who are not researchers, and who are not affiliated with the institution should collectively make up at least one quarter of IRB membership.[11]This would be an important step in dealing with nonfinancial conflicts of interest. A second step can be expanding audits of ongoing trials. Analysis of the problems leading to deaths indicates that excessive zeal in trying t complete the trial. Disclosure is the golden rule in managing conflict of interest. To judge whether one is in effect of conflict of interest can be revealing to ask the question: "would I feel comfortable if patient found out about my interest?" when the answer is "no", at a minimum discloser is sensible. The role of disclosure of financial relationships to participants and others has been reviewed and recommendations proposed[12] Among these recommendations, it was noted that because many participants may not fully appreciate the impact that financial relationships might have on research design, conduct, and analysis, in addition to requiring disclosure, IRBs and others should "play a significant role in deter- mining the acceptability of these relationships."[12]

A nongovernment and non-profit organization the Council for International Organization of Medical Sciences (CIOMS) has been established by World Health Organization (WHO) and United Nations Educational, Scientific and Cultural organization (UNESCO) in 1949.[13] In 1993, the publication by CIOMS mentioned that the product under study should be reasonably available to the community and country that hosted the study, and in case of exception, proper justification and agreement by all concerned should be submitted before start of the study. : "the sponsor and the investigator shall make every effort to ensure that any intervention or product developed or knowledge generated, is made reasonably available for the benefit of the population or community".[14] The declaration of Helsinki points out that the post trial access is a benefit only to subject, while CIOMS extends to include community and population. The CIOMS proposes that the documentation on post study availability should be incorporated into the Informed consent form, while Declaration of Helsinki demands that it should be documented in protocol.

The universal Declaration on Bioethics and Human Rights (UNESCO, 2005) includes the text: "benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries". However, the benefits can take many forms, not only post trial access to investigation drug. Unfortunately there is no firm consensus regarding how best to respond because many other difficult questions arise for regulatory and policies with the post trial access of study drug. Should subjects have priority access over others? Do they have any legally or ethically valid claim for continued access of investigation drug? Who will bear costs if there is an obligation to provide subject with post study access, whether sponsor, investigator, CROs, medical centres where the research is conducted? In the ICMR guidelines 2000, there is no separate mention of PTA. However, the principle of non-exploitation deals with the kind of remuneration, care and

compensation in case of study related injury. In the revised guidelines issued in 2006 (Ethical guidelines For Biomedical research On Human participants: ICMR 2006) under the principle of maximization of public interest and distributive justice, states that: "Whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged, and in particular, the participants themselves and or the community from which they are drawn". It refers to the Helsinki Declaration and quotes the same (2004) on PTA.[15] Study participants who have risked harm or experienced other research related burden for good of clinical trial may highly value continued access to study drug, even if it offers marginal therapeutic improvement.

While investigator may have less regards for participants' needs and place more value on ensuring that the trial continues to a valid statistical stopping point. Investigator might want to conduct new trial with different subject to reasonable degree of scientific acceptability. The sponsors may have fewer concerns about subjects' needs for business reasons. Sponsors perspective in providing access enables collection of data that lengthens product's market-life and improves company's public image but also reduces its share-holders' profits and funding of other projects. The commitment for post trial access reduces the incentives to conduct research due to financial constrains especially for academic projects. Sponsors lack power to make unilateral decisions about PTA, priorities of agencies providing health care in host country may differ from sponsor[16] Meanwhile regulatory may focus regulatory review on whether trial data justifies approving the new drug for marketing.

Few studies have been conducted on post-trial access and related issues and most of them are on HIV/AIDS trials. A qualitative study, carried out through focal groups in Kenya, with 89 subjects (potential patients for HIV/AIDS studies, researchers and administrators) has brought, as conclusion, that it would not be reasonable to discontinue therapy after studies in HIV/AIDS patients, except in fully justified cases.[17] A study carried out through interviews with presidents and members of research ethics committees (RECs), as well as researchers and research participants, evaluated the ethical aspects related to conducting clinical trials outside the United States. Sixty-five of 94 questionnaires sent to members of RECs returned, as well as 117 of 159 sent to researchers and 359 of 510 sent to research participants. Eighty-three percent of research participants (of which 43% were from Latin America, Brazil included), 29% of RECs members and 42% of researchers said the drugs should be provided for all infected people worldwide, if proven beneficial. Most research participants from Europe and Latin America said that the drug should be continued, while those from North America, Australia and Thailand said that the drug should be made available at a price that a middle-class individual could buy.[18]

A systematic review of clinical studies enrolled in international registries, from 2004 to 2007, was carried out by Cohen et al.[19] involving HIV/AIDS, malaria and tuberculosis. Of the 312 studies that were included, the majority in developed countries (56%), with 28% being sponsored by pharmaceutical companies, only 4 (1.3%) mentioned post-study provisions: one mentioned the post-study drug would be provided by the governments of the respective countries; another,

that the participants who became infected with HIV during the study would receive counselling and education about the infection/disease and access to necessary healthcare, including free-of-charge antiretroviral drugs, if indicated. Sofaer et al.[20] described the opinion of 93 individuals who participated in clinical trials in chronic diseases in the United States. In this study, patients were divided into 10 focal groups. Many participants felt that researchers, sponsors and insurance companies should share the post-trial obligations. Others commented that no care or drug should be necessary after the research, but there was an almost general agreement that patients should receive information about the study and its results. The authors conclude by suggesting that the debate on post-trial obligations must go beyond the issue of the test drug. Reviewers and commentators have worried about the possibility of undue inducement from continued provision of treatment. If continued access to treatment is guaranteed, the treatment access may be so attractive that an individual might be unable to refuse participation even if he or she wanted to.[21]

Even if the rationale for assuring continued treatment is compelling, the question of who should be responsible for assuring this and how it should be accomplished remains. It has been argued that if pharmaceutical companies and sponsors are made solely responsible for assuring continued access to beneficial treatment, this requirement could serve as a major disincentive for companies to engage in certain kinds of research.[22] This could also jeopardize the future of research in places with limited health care access, especially for diseases that might require chronic or expensive treatment.[23] Commentators worry about the possibility of dampening research in developing countries where new treatments are needed the most.[24]

However, Post trial access to participants of phase II trial is unarmed where the benefit of the investigational product is still at risk. The benefit of drug is always a relative term in many clinical trials, and it often difficult to quantify the benefit of study drug compared to the standard treatment which forms the basis to advocate it during the post trial periods.[25] Phase I to III trials do not provide proof of safety but evidence. It is observed many a times that after the drug introduced in larger population, the rare adverse effects are made known. In such case, it is not ethical to prolong exposure of investigational medicine, when standard treatment is available. Again what if drug is not approved? It is ethically not acceptable to expose participants to ineffective drug for extended duration. Clinically the claim for post trial access is more valid when no alternative effective and safe treatment is available. The extension of benefits leads undue inducement and participants joining the trial to obtain access to medication.[25]

Subsidized access to drug that have been proven successful might be the best alternative to benefit to the host community and it can reduce inequalities between resource poor and rich countries. It can ensure faire division of burden and benefits between host countries and that sponsor the trial. Sometimes more than the benefits to participants, the community may be given benefits in an indirect way such as clinics and giving education on maintain good health practices, improving their living conditions etc.[26]

In last few years, use of placebo in clinical trial has been criticized a lot and many authors have argued that placebo controlled trials are unethical when known therapy is available, not considering the consequences or the condition of deferring treatment. Some have emphasized that the comparison of new treatment with old treatment is sufficient and disputed the value of placebo controlled trials.

If we take the requirement of Declaration of Helsinki literally that all patients should receive best proven therapeutic method, it will bar all clinical trials, including historically controlled trials, because when effective treatment exists the patients taking study drug are not receiving best proven treatment.[27] According to Temple and Ellenberg, many classes of drugs considered as effective cannot be demonstrated to be superior to placebo in 30 to 50 % of studies. The problem could be the small response that varies among population, study samples that improve spontaneously, unresponsive to drug, insufficient compliance or concomitant medications or any other reasons.[28] In such circumstances, they believe that apparent equivalence of a new drug to a standard medication may not imply that the new drug is effective, because there is doubt whether standard treatment is effective, where placebo controlled trials are needed to demonstrate new medications safety and efficacy profile.

Patient willing to participate in placebo controlled trial must provide fully informed consent, and patient must be informed of existence therapy and must be able to understand the possible side effects of new therapy with camper to available one. These concerns apply as much to the patient's decision to forgo known effective treatment and risk exposure to a potentially ineffective or even harmful new agent in an active-control trial as to a decision to accept possible persistence of symptoms in a placebo-controlled trial. So, the problem is not unique to placebo controlled trial. Although in many cases application of this standard will be fairly straightforward, in others it will not and there may be debate about the consequences of deferring treatment.[27] For these reasons, placebo controlled trials may be conducted ethically even when effective treatment is available, as patient will be adequately informed about alternative therapies and will not be harmed by participation. On other hand, the ability to conduct placebo controlled trial in given situation does not mean that placebo controlled trial should be carried out over when effective therapy exists. Researchers might prefer active treatment to be given to every participant. Now here the question is why placebo controlled trial are needed and often cannot be replaced by active control trials. The limitations of active- control equivalence trials that are intended to show the effectiveness of a new drug have long been recognized and are well described,[29, 30, 31] but are perhaps not as widely appreciated as they should be. A recent proposed international guideline on choice of control group addresses this issue in detail.[30]

In placebo controlled trials patient s are not untreated all the time. Sometimes investigational drug can be assessed by using add-on study design, where all patients will be given standard therapy and will be randomly assigned to placebo or new drug.[30, 32] Such design can be use for the indications where standard therapy cannot be omitted ethically, for example cancer, epilepsy, heart failure etc. 'Randomized withdrawal' and 'early escape' study designs limit the duration of

placebo exposure without compromising the rigidity of study. In a randomized withdrawal study, apparently responsive patients are given an investigational therapy for a period and are randomly assigned to receive placebo or to continue active therapy. In an "early escape" study, patients are randomly assigned to receive new drug or placebo, but a well defined treatment failure end point is used as the basis for changing therapy in patients who are not benefiting from their initially assigned treatment. This design was initially proposed by Amery[33] as a way of avoiding extended placebo treatment of patients with angina pectoris. A particular value of the randomized withdrawal study is that it demonstrates a persistent effect for durations that would be difficult to study in placebo-controlled trials.

The another argument in favour of conducting a PCT is based on a principle of ethics, that of utility, which is to always produce the maximal balance of "positive value" over negative value. PCTs provide quicker and more reliable answers to scientific questions. However, using a utilitarian calculation to justify placebo use in conditions that result in morbidity, and/or mortality, violates the principle of beneficence, even if consent is obtained. [34] Ethical principles sometimes conflict with the scientific rigour of the trial: this argument was based on the assumption that PCTs are methodologically superior and hence beneficence and informed consent may be trumped by "scientific rigour, justice and social utility."[35]

CONCLUSION

In research context of the primary interest is scientific knowledge where as in clinical practice the primary obligation of physicians is to their patient. A secondary interest may be financial, also consist personal prestige and academic promotion and recognition. The research interests, although often is concordance with patient' interests, are secondary to clinical care and may conflict with it. Many concerns exists the ability of clinical investigator to provide the information to patient regarding participation in trial in such a way that he/she to recognize the distinction between therapy and research.

The decision on providing access to investigational drug after completion of clinical trial should be based on two dimension, SAFETY and EFFICACY assessment. All clinical trials have its own assessment based on disease and study populating as per their specific needs. Therefore, the post trial obligation cannot be generalized and be considered the same in all trials. Nonetheless, it should be assured that relationship between patient and physicians during study must be always terminated with the respect and responsibilities.

Placebo controlled trials are very important where used ethically, and if they are scientifically desirable they should only be conducted if they are ethically acceptable, no matter where they are conducted. Historical controls are not useful for current studies as diagnostic and efficacy criteria, and concept of disorder has changed for certain diseases. To avoid unnecessary risks, placebo controlled trials should be conducted in highly controlled setting with adequate follow

up and well defined stopping rules. With all these safeguards, the use of placebo will generally benefits and override any ethical uncertainties in short term studies.

LIMITATION

The main limitation of this study is a small sample size and respondents are from the industry. A large survey with adequate sample size including patients group required to validate the survey findings.

CONFLICTS OF INTEREST

We certify that there is no conflict of interest.

REFERENCES

1. Adequate and well-controlled studies. Code of Federal Regulations, 21 Part 314.126. Revised as of 1 April 2000. Washington, DC: U.S. Government Printing Office; 2000.

2. Amery W, Dony J. A clinical trial design avoiding undue placebo treatment. J Clin Pharmacol. 1975;15:674-.9.

3. Benatar SR, Fleischer T. Ethical and policy implications of clinical drug trials conducted in developing countries. Harvard Health Pol Rev. 2005;6(1):97-105.

4. Council for International Organizations of Medical Sciences (CI- OMS), in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects. CIOMS, Geneva; 2002.

5. Cohen M, O'Neill M, Joffres M, Upshur G, Mills E. Reporting of informed consent, standard of care and post-trial obligations in global randomized intervention trials: a systematic survey of registered trials. Dev World Bioeth. 2008;9(4):74-80.

6. Ethical and policy issues in research involving human participants. Vol. 1. Bethesda, Md.: National Bioethics Advisory Commission, August 2001. https://bioethicsarchive.georgetown.edu/nbac/human/overvol2.html, accessed on 20 Sep 2014.

7. Ellenberg S, Temple T. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: Practical issues and specific cases. Ann Intern Med. 2000;133:464-70.

8. Ezekiel J. Emanuel, Ending Concerns About Undue Inducement, 32 J.L. MED. & ETHICS 100 (2004) (Abstract).

9. Grady C. Ethics of international research: what does responsiveness means? Ethics J Am Med Assoc. 2006;8(4):235-40.

10. Hillman J, Joseph A, Mabel R, Sunshine H, Kennedy D, Noelher M. Frequency and costs of diagnostic imaging in office practice: a comparison of self referring and radiologist referring physicians. N Engl J Med 1990;323:1504-8.

11. Helen Frankish, WVMA Postpones Decision to Amend Declaration of Helsinki, 362 THE LANCET 963 (2003) (Abstract).

12. International Conference on Harmonization: choice of control group in clinical trials. Federal Register. 1999;64:51767-80.

13. Jones B, Jarvis P, Lewis A, Ebbutt F. Trials to assess equivalence: the importance of rigorous methods. BMJ. 1996;313:36-9. 32. Martin T, John D, Reynolds M, Andrew M, Henry M, When placebo controlled trials are essential and equivalence trials are inadequate. BMJ. 1998;317:875-80.

14. Jintanat Ananworanich et al., Creation of a Drug Fund for Post-Clinical Trial Access to Antiretrovirals, 364 THE LANCET 101 (2004) (Abstract).

15. Levinsky G. Sounding Board. Nonfinancial conflicts of interest in research. N Engl J Med 2002;347:759.761.

16. Marshall E. Penn report, agency heads home in on clinical research. Science 2000;288:1558-9.

17. New Delhi: ICMR; 2006. Ethical guidelines for biomedical research on human participants.

18. Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Moral Standards for Research in Developing Countries. From “Reasonable Availability to “Fair benefits”. Hastings Center Report 2004;34(3):2-11.

19. (Pace C, Grady C, Wendler D, Bebchuk D, Tavel A, McNay A, et al. For the ESPRIT Group. Post-trial access to tested interventions: The views of IRB/REC chair, investigators, and research participants in a multinational HIV/AIDS study. AIDS Res Hum Retroviruses. 2006;22(9):837-41 (Abstract).

20. P. G. De Roy, Helsinki and the Declaration of Helsinki, 50 WORLD MED.J. 9 (2004) (Abstract).

21. Resnik DB. The ethics of HIV research in developing nations. Bioethics. 1998 Oct;12(4):286-306.

22. Rochon A, Gurwitz H, Cheung M, Hayes A, Chalmers C. Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. JAMA 1994;272: 108-13. 7. Elks L. Conflict of interest and the physician-researcher. J Lab Clin Med 1995; 126:19-23.

23. Sachs B. Going from principles to rules in research ethics. Bioethics. 2011;25:9.20.

24. Sanmukhani J, Tripathi B. Ethics in clinical research: The Indian perspective. Indian J Pharm Sci.2011;73:125.30.

25. Sackett L, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996; 312:71-2.

26. Steinbrook R. Protecting research subjects . the crisis at Johns Hopkins. N Engl J Med 2002;346:716-20.

27. Sofaer N, Strech D. Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: A systematic review. Public Health Ethics. 2011;4:160.84.

28. Shaffer N, Yebei N, Ballidawa B, Sidle E, Greene Y, Meslin M, et al. Equitable treatment for HIV/AIDS clinical trials participants: A focus group study of patients, clinician researchers and administrators in western Kenya. J Med Ethics. 2006;32(1):55-60.

29. Sofaer N, Thiessen C, Goold D, Ballou J, Getz A, Koski G, et al. Subjects' views of obligations to ensure post-trial access to drugs, care and information: qualitative results from the Experiences of Participants in Clinical Trials (EPIC) study. J Med Ethics. 2009;35:183-8.

30. Temple T, Ellenberg S. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. Ann Intern Med. 2000;133:455-63.

31. Thompson F. Understanding financial conflicts of interest. N Engl J Med. 1993; 329:573-6.

32. Wilkinson P. "Self referral": a potential conflict of interest. BMJ 1993;306:1083-4.

33. Weinfurt P, Hall A, King P, et al. Sounding Board: disclosure of financial relationships to participants in clinical research. N Engl J Med 2009;361:916.921.