**RESEARCH ETHICS**

**Survey on Perceptions of Indian Investigators on Research Ethics**

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**Abstract**

**Introduction:**

The last decade has witnessed globalization of drug development with early phase studies being increasingly placed in the developing world. Whether research related ethical principles around informed consent, adverse event (AE) reporting, post trial drug commitments and others are being observed, merits evaluation.

**Methods:**

A specially designed survey questionnaire was served to 29 investigators in India, having prior experience of participating in drug development studies with pharmaceutical companies. The survey included questions on investigator profile, study design, informed consent process, safety reporting, patient and physician compensation, post trial drug commitments among others.

**Results:**

Most respondents had nearly two decades of clinical experience. Majority believed that the research they conducted was relevant to the needs of society, but wanted common research goals established between the sponsors and the community. All investigators cited their expertise, reliability, patient pool, and low costs as the principal reasons for greater placement of studies. However, very few investigators felt that all their patients in studies were “truly autonomous”. Most investigators indicated confidence in the adverse event reporting ability and expressed satisfaction with their Ethics Committees. A third of investigators accepted some form of conflict of interest between their role as a physician and researcher. Opinion was divided regarding satisfaction with the post trial drug commitments of the sponsor companies.

**Conclusion:**

The survey revealed a good understanding of the ethical issues around conduct of clinical research in a developing country. The sooner ethical institutions and practices are fortified, the better it is for communities, patients, investigators and pharmaceutical sponsors.

**Key words:** Clinical Research; India; Research Ethics;
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Methodology

The research was based on interviewing investigators in India experienced in industry related drug research. Physicians were selected based on extensive research experience in Phase II/III drug development studies. They were instructed that their response should reflect their actual experience during study conduct.

Based on the information garnered from the clinicaltrials.gov website and other informal sources, it was estimated that there were approximately 400 sites involved in drug development studies in India. The aim was to cover about 5% of these sites/investigators in this pilot survey, and hence it was decided to serve the questionnaire to 25 to 30 investigators. The aim of this pilot study was to recognize trends and generate hypothesis related to medical ethics in trial conduct, rather than to test any preconceived notions.

A special questionnaire was constructed to facilitate the conduct of this study. The questions pertained to the identification of key ethical issues or barriers in conduct of drug development research, with a special emphasis on the Informed Consent (IC) process. The survey comprised of 49 questions on various aspects like investigator profile, study design, healthcare equity issues at the hospitals/sites, study participation characteristics, IC process, safety reporting, investigator compensation, local ECs /IRBs (institutional review boards), post trial drug commitments and eliciting best practices and their suggestions.

The process of formulating and selecting the questions was complex. Initially all likely questions related to research ethics were noted and 60 questions selected. A draft questionnaire was prepared and piloted with two senior and experienced investigators in Mumbai, India. This piloting was done as a “formal interview” process; this resulted in omission/ modification of several questions for better comprehension. The final questionnaire arrived at, was more easily understood, and was served to the investigators in the study.

Most questions were either “Yes/ No” or multiple choice format to ensure that the responses could easily be aggregated to recognize trends and behaviors. There were very few subjective questions. None of the questions asked for any study specific or patient specific data.

The survey was conducted with the help of the clinical operations staff of Pfizer India. The investigators were identified from across the country, including both private and public hospitals. They were briefed on the scope and purpose of the survey. Confidentiality was assured and that the data would be analyzed and presented under grouping of investigators. A written consent was obtained from the investigator.

The project protocol, investigator letter and the survey questionnaire were approved by an Independent Ethics Committee in India.

Results and Discussion

Investigator Characteristics

Of the 29 investigators that responded, the majority (72%) belonged to the private sector and generally treated relatively affluent patients (Table 1).

Table 1 Investigator Characteristics

| Sector | Percentage (n) |
|--------|----------------|
| Private| 72 (21)        |
| Public | 28 (8)         |

The industry has been active in placing studies more often in the large private hospitals because of less bureaucracy, faster approvals, more space, and keenness of physicians to participate in clinical trials, though there are many more patients seen in the government sector. However patients participating in clinical trials in India, do not necessarily all come from poor and illiterate families, as is generally believed.

The study had a fairly even spread across different specialties namely psychiatrists, oncologists, ophthalmologists, urologists, cardiologists, internists, endocrinologists, chest specialists, and rheumatologists. The majority had over two decades of clinical experience but around 10 years of research experience and nearly half had served on an EC/ IRB (Table 2).

Table 2: Research Experience

| Research Experience (Yrs) | Percentage (n) |
|---------------------------|----------------|
| 1 - 5                     | 17 (5)         |
| 6 - 10                    | 38 (11)        |
| 11 - 15                   | 17 (5)         |
| 16 - 20                   | 3 (1)          |
| > 20                      | 24 (7)         |

Study Design and Participation

There has been increased drug development activity in India over the last decade and all respondents affirmed having being increasingly approached by the pharmaceutical companies to do clinical trials. The reasons provided were the reliability and experience at their sites, good availability of patients and low costs.

82% of the investigators opined that the drug development studies were relevant to the needs of their country. Majority also believed that the active comparator used in India was usually the same as in the developed world.

Most investigators felt that there were inequities in healthcare between developing and developed countries, and
90% believed that the pharmaceutical companies should set common research goals for all communities or countries.

**Informed Consent Process and Patient Awareness**

This was the largest section in the survey questionnaire and was designed to bring out the possible pitfalls in the IC process in a developing country like India, where many research subjects are expected to be indigent or illiterate, and therefore more likely not to be ‘truly autonomous’.

86% of the investigators stated that their patients had full understanding that there was no compulsion to participate in the study. We may be over estimating independence on part of the patients since this survey was based on physician interviews rather than patient interviews and involved physicians from large metropolitan hospitals working with large pharmaceuticals sponsors and therefore had an opportunity of sound ethical training.

Regarding consent withdrawal following randomization, 68% of investigators felt up to 10% of patients withdrew at their sites with the common reasons being adverse events (AEs), inconvenience of adherence to the protocol/study visits, lack of efficacy, inconvenient procedures, and study phobia. The reassurance to the patient that he/she can leave a study at any time is a very assuring factor and one of the mainstays to ensure the autonomy of the patient (Table 3).

**Table 3: Withdrawal Reasons**

| Important Reasons for Withdrawal         | Percentage (n) |
|-----------------------------------------|----------------|
| Toxicity                                | 19 (5)         |
| AEs                                     | 23 (6)         |
| Availability of Investigational Product in the market | 4 (1)         |
| Fear                                    | 15 (4)         |
| Fear of Randomization                   | 4 (1)          |
| Inconvenience of Procedure              | 23 (6)         |
| Inconvenience to adhere to protocol specific visits and investigation | 35 (9)         |
| Social Reason                           | 12 (3)         |
| Alternative treatment                   | 4 (1)          |
| Unsatisfactory improvement/lack of efficacy | 23 (6)       |
| Lack of initial understanding/awareness about the nature of trial | 4 (1)         |

52% of the investigators felt that the present IC process was more designed to cover the legal compliance, rather than a helpful tool to truly inform and educate the patient regarding study participation. Only 10% of sites always involved a social/community worker. Majority of the sites had never used any modern techniques like audio visual aids or IC process recordings.

All the investigators felt that a reasonable daily/traveling allowance should be provided to the participating patients as the study may entail numerous visits. Most investigators also felt the need to reassure their patients they will not have to pay from their pockets and that a reasonable compensation would either not, or very rarely, lead to an undue influence on patient participation.

65% of the respondents accepted that patients agreed to participate in studies at their site due the fact that they could have better access to physicians and/or better medical care.

As expected, invasive procedures and repeated blood samples were cited as the most common reasons for negatively impacting the IC process. 40% of the investigators also believed that illiteracy has a negative impact. Curiously, low social class and female sex were not mentioned as common factors negatively impacting the IC process in this survey.

**The Truly Autonomous Patient**

Regarding the question of truly autonomous patient, only 18% investigators believed that all their patients in clinical trials, represented truly autonomous patients (Table 4).

| Percentage of truly autonomous patients | Percentage (n) |
|-----------------------------------------|----------------|
| 100                                     | 18 (5)         |
| 90-99                                   | 39 (11)        |
| 70-89                                   | 14 (4)         |
| 50-69                                   | 18 (5)         |
| Less than 50%                           | 7 (2)          |
| Don't know                              | 4 (1)          |

**Safety Reporting**

The ability and inclination of patients in developing countries to report AEs in clinical studies has been controversial.

In this survey the investigators showed a lot of confidence in the patients’ ability and will, to report the AEs faithfully and promptly, at their sites. The response was similar if one factored the socioeconomic status as well.

**Investigator Compensation**

Although majority of the investigators did not feel that there would be a conflict, few that did were very candid in providing the reasons. Some examples were that protocol prohibits use of a concomitant medication that may benefit the patient, enrolling a patient merely because he meets eligibility criteria though the study drug may not be ideal for him etc. The reasons were similar to what might happen as a conflict in most parts of the developed world. Hence, research in a developing world setting does not in itself have a special impact on this conflict of interest, which probably transgresses political and cultural borders.\(^{[6]}\)
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Ethics Committees

Although most of the investigators (83%) were satisfied with the constitution and working of their ECs, some did have some suggestions to improve manpower, secretarial help, space, training, and orientation towards local needs.

The ECs very rightfully in most cases asked questions related to the IC process and post trial drug commitments of the sponsor company. There were differences in the way ECs responded at different centers. But this is in line with the international experience. The commonest causes cited for variations in the EC approach is the local variations in medical care, culture, social issues, and a general lack of guidance to ECs as to what constitutes proper compensation and post trial drug commitments.\(^{(9)}\)

Post Trial Drug Commitments

What came through was that most investigators thought that their research did fundamentally address the community needs. Most felt that the Pharma companies did launch the products, (unless the drug failed development) but most also felt that they were high priced, and common unaffordable by majority of patients. There was a mixed response to their satisfaction level on the post trial drug commitments and half the investigators felt that the supply of free drug should continue to the responding patients till the drug is commercially available, while a third of them thought that it should be made available free of cost for the rest of their lives.

There is thus a case that that there must be an assurance of reasonable availability of a study drug if it is proven to be safe and effective.\(^{(10)}\) How are the companies fairing in this respect is a question that needs to be worked out.

It is important that sponsor companies, regulators, and academic investigators come together and have a discussion on this contentious issue and draw the guidelines that sponsor companies are expected to follow, in relation to the post trial drug obligations, and if there are any legal safeguards to be built for the patients, then that should also be done.

Limitations

In recent years, there has been substantial debate about the ethics of research in developing countries. In general, the controversies have centered on 3 issues: first, the standard of care that should be used in research in developing countries; second, the “reasonable availability” of interventions that are proven to be useful during the course of research trials; and third, the quality of informed consent.\(^{(11)}\)

This survey does have limitations of self reporting as the responses would be subjective and may not be reflective of true/prevailing practice patterns. However this pilot survey does provide some insight regarding physicians’ perceptions on ethical research practices.

Conclusions

This survey revealed that the investigators were aware and observant of the ethical principles in clinical research and revealed interesting patterns on the investigators’ experience in India, but the overall theme which emerged was the dawn of a new era in ethical clinical research.

What is therefore important is to introduce early in the curriculum of medical students a subject on drug development, which includes a wide exposure to clinical research related ethical issues.

A larger survey involving physicians from smaller cities, and those who have participated only occasionally in drug development research, is likely to throw up, many other contentious ethical issues.

The important learning lesson is that drug development research is here to stay in the less developed world. The earlier ethical institutions and practices are fortified, the better it is for the communities, patients, investigators and the pharmaceutical companies.

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