

Differences in the Collection of Clinical Trial Safety Information: United States Versus India

by

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Abstract

Clinical or human trials are structured and sequenced research on human subjects that aim to provide effective and safe treatment options to its participants. Clinical trials are required to adhere to regulatory requirements, with major emphasis on subject safety, as they involve the testing of new chemical entities in human subjects. Thus, the data collected from clinical trials are very crucial, and are the basis for determining the drug's safety and efficacy. The safety of a drug or new chemical entity depends upon several factors, such as patient population, risk–benefit ratio, therapeutic area, and the unique structured protocol developed specifically for that drug. Most importantly, it is dependent upon the safety regulations and guidelines in different countries, and the emphasis placed on collecting, reporting, and analyzing this safety data. This study outlines the basic elements for carrying out clinical trials in developing countries like India, with respect to its diversity and population. It also provides insights into the increase of serious adverse drug events and unethical practices taking place in India due to various factors that include regulatory barriers, cultural differences, and illiteracy. However, the main limitation to this study was the difficulty in acquiring information on adverse drug events, as this information is purely confidential, although it could be studied with publicly available information from relevant sources.

Introduction

Clinical trials, also known as drug trials, are systematic scientific tests done in healthy human volunteers as well as patient groups. These tests are carried out in four different phases, each of which has their own significance. Prior to the inception of clinical trials, a series of clinical tests, known as pre-clinical tests, are carried out wherein the new chemical substance is tested in both *in vitro* and *in vivo* environments, followed by testing in human volunteers (1). Parameters, like safety and an initial safe starting dose for human trials, are tested in this phase. The second phase is where human volunteers are tested for parameters like safety and therapeutic index of the new chemical substance with respect to drug dosage. The third phase is of utmost significance as it determines the efficacy of the drug over a long period of time compared to the earlier phases. This phase also helps in determining adverse drug events and drug interactions that may occur, which paves a way for the therapeutic success of the drug. Unlike the earlier phases of the clinical trials, phase four is most important as it studies the long-term effectiveness of the drug in human subjects in a non-medical and normal environment (2).

Clinical research has come a long way from conventional treatment to contemporary therapies. Over the past decade, biopharmaceutical and pharmaceutical industries have witnessed a large pool of complexities that have affected their operations and profits. Some business reviews highlight that the current business models have become inefficient leading to economic instability, and are operationally unsuited to churn out innovative treatments; these industries have recognized the opportunities and advantages in emerging markets like India (3). India's clinical research landscape has been undergoing a metamorphosis. Statistics show that India is now ranked third just behind China and the United States, in terms of most favored clinical trial destination (4). However, conducting research in resource-limited countries is a major challenge

in itself. In addition, setbacks due to differences in geographical time zones, as well as multi-cultural and multi-lingual differences, can occur. Moreover, factors like insufficient clinical operational training, site personnel's lack of information on guidelines of host country, and poor quality of monitoring sites with respect to the safety aspects of the clinical trial, may affect the conduct of the clinical trial (5).

Research Question

Are there differences in the adverse event (AE) profile of drugs developed in the United States and India? If so, what are the reasons for these differences?

Methodology

A literature review was carried out to understand if more patients suffer adverse drug effects from clinical studies conducted in India than in the United States. The AE profile derived from clinical trials in similar populations in India and the United States was compared. Factors related to the greater incidence of adverse events in India were investigated.

- To address the research question, an extensive literature search was conducted to identify drugs that have been tested in both countries. The literature review also helped to clarify the theoretical and research issues pertaining to the research question.
- Websites such as www.clinicaltrials.gov provided information about drugs and the studies that have been conducted on them in various countries. Among these, drugs were selected for which clinical trials were conducted in both the United States and India, as they would provide information on the extensive research regarding patient safety.
- Clinical trial data collected in the United States for the selected drugs were obtained from various websites, journal articles, research publications, and newspapers. These data were further compared with those from clinical trial data generated in India, which was obtained from various websites and personal communications.
- The comparison of AE data for selected drugs from both countries was used to determine factors (if any), that resulted in adverse events, and to develop recommendations which may help address concerns associated with the possible increase in the occurrence of serious adverse events (SAEs) in clinical drug trials conducted in India.

Results

Multicentric trials conducted in the United States and India were chosen for the review and understanding of safety measures in clinical trials in India. Specifically, three studies were reviewed that were conducted with identical protocol, intervention, and randomized design in both countries.

Ixekizumab (LY2439821) study sponsored by Eli Lilly and Company

Generic Name - Ixekizumab (Monoclonal antibody-Inetrleukin-17 inhibitor)

This study was conducted in participants with moderate to severe psoriasis. It is officially entitled, “A dose ranging and efficacy study of LY2439821 (an anti-IL-17 antibody) in patients with moderate to severe psoriasis.” The study was an interventional, Phase 2, randomized, parallel, double-blind, safety or efficacy (end point classification) study whose primary purpose was treatment (6). The following research issues were addressed:

- The safety of ixekizumab (LY2439821) and any associated side effects.
- The ability of ixekizumab to improve the condition of patients suffering with psoriasis.
- The dose of ixekizumab that should be given to participants.

The study was designed to evaluate the safety, clinical activity, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of ixekizumab when given by subcutaneous (SC) injection. The active drug and placebo drug groups were compared in adults with plaque psoriasis. The study duration (not including the entry period) was approximately 240 to 264 weeks. The study consisted of two parts. Part A was a randomized, double-blind, placebo-controlled, parallel-group, dose ranging study where participants were evaluated at week 12 for the primary purpose (treatment). Between weeks 20 and 32, participants with less than 75%

improvement in their Psoriasis Area and Severity Index (PASI) score compared to baseline were eligible to begin Part B, which was an optional, open-label extension study. Participants in Part B received SC injections of 120 mg ixekizumab every 4 weeks through week 236. The study consisted of a treatment period of 20 weeks during Part A. For patients who did not participate in Part B, a follow-up period of 12-20 weeks was required. Participants who completed Parts A and B had a total study participation of approximately 240 to 264 weeks (4). The primary endpoint was the proportion of patients with a reduction in the PASI score by at least 75% at 12 weeks. Secondary endpoints included the proportion of patients with a reduction in the PASI score by at least 90 or 100%. The results included the percentage of patients with a reduction in the PASI score by at least 75% was significantly greater with ixekizumab than with placebo. Similar was the percentage of patients with a reduction in the PASI score by at least 90% and even 100% (7).

In the United States, 142 patients with chronic moderate to severe plaque psoriasis were randomly assigned to receive SC injections of 10, 25, 75, or 150 mg ixekizumab or placebo at 0, 2, 4, 8, 12, and 16 weeks. In groups (ixekizumab and placebo groups), AEs such as hypertriglyceridemia (reported by placebo group), peripheral edema, hypersensitivity, headache, and urticaria were reported in few patients, who were subsequently withdrawn from the trial (8). However, the overall frequency of AEs was low, and none of the groups reported a SAE. As aforementioned, ixekizumab was given at doses of 10, 25, 75, or 150 mg. There was significant improvement in patients present in the treatment arm who received the doses 25, 75 and 150 mg respectively. However it was found that patients who were administered lower dose of ixekizumab (10mg) showed less response. These data suggests that ixekizumab would be safe for patients with chronic moderate to severe plaque psoriasis, and could represent a new treatment approach for patients with this condition (9).

Since the study was a multicenter study with identical protocols, it was conducted with the same procedures in India. There, the study consisted of an entry period of up to 30 days with 125 patients who were randomized or enrolled to receive SC injections of the same doses. Further the Phase II trials were already considered to be safe in U.S.A, however yet to be known in India. The number of AEs reported in India was more than that reported in the United States, and included neck pain, fever, skin aberration (skin peeling and sealing), fractured right arm, and inflammation of skin on the arm, intestinal infection, throat infection, and thrombocytopenia. The severity of the AEs was also greater in this population of patients, and each AE lasted a minimum of 2-5 days. In addition, SAEs were reported; many patients were hospitalized and some died (10) (See Table 1).

Table 1: AE data for ixekizumab from the United States and India.

S.No	Country	Number of patients enrolled	AEs	SAEs
1.	United States	142	Peripheral edema (4) Hypersensitivity (14) Head ache (9) Urticaria (4)	None
2.	India	~130	Neck pain (3) Fever (14) Skin Aberration (26) Fracture of right arm (2) Inflammation of skin (12) Intestinal infection (6) Throat infection (5) Thrombocytopenia (1) Anxiety (7) Depression (11) Seizures (1)	1.Hospitalization 2.Death

Restasis study sponsored by Allergan

Cyclosporine ophthalmic emulsion 0.05%, whose brand name is Restasis, is used to treat dry eyes (11). It increases tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. A study entitled, “Study of two formulations of cyclosporine ophthalmic emulsion in patients with dry eye” was conducted with the same protocol in the United States and India. This was a Phase I, randomized, parallel, double blind, interventional, safety study that consisted of two phases, namely, a parallel-group phase and a paired eye phase. The purpose of this study was to evaluate the safety of two formulations of cyclosporine ophthalmic emulsion in healthy adults (parallel-group phase) (12). The parallel group phase enrolled healthy volunteers who were given cyclosporine ophthalmic emulsion formulation A and cyclosporine ophthalmic emulsion formulation B. This was followed by a paired-eye-phase, which determined the safety and tolerability of the two formulations of cyclosporine ophthalmic emulsion compared to Restasis. The paired-eye phase enrolled patients with dry eye symptoms, and the study began after the parallel group phase was completed. Table 2 describes the combined treatment and dosage chart for the paired-eye phase of the study (13).

Table 2: Treatment chart for Restasis (paired-eye phase, combined dosage regimen).

Treatment Arm	ARM 1	ARM 2
Recommended Dosage	0.05% Restasis emulsion mixed with ophthalmic emulsion A.	0.05% Restasis emulsion mixed with ophthalmic emulsion B.
First Recommended dose administration Time	6:00 a.m.	6:00 a.m.
Wait Interval	12 hours	12 hours
Second recommended dose administration time	7:00 p.m.	7:00 p.m.

The results of the clinical trials conducted in both countries were satisfactory. In the United States, the number of patients treated with formulations A and B had a greater number of adverse events compared to patients who received Restasis (14). Although AEs occurred, the severity was minimal. The most common AE reported was ocular burning; other AEs included eye pain, stinging, visual disturbance, and epiphora (15). In India, SAEs resulted in hospitalization due to such conditions as hypertension, angina, and ear infection. In addition, a 36-year-old male individual died (See Table 3).

Table 3: AE data for Restasis from the United States and India.

S.No	Country	AEs	SAEs	Number of patients enrolled
1.	United States	Ocular burning (16) Eye pain (2) Stinging feeling (palpitation of eye) (21) Epiphora (3) Throat pain (1)	Hospitalization due to angina (1)	44
2.	India	Ear infection (24) Hypertension (2) Rashes (5) Itching (7) Dizziness (2) Anxiety (11) Eye discharge (26) Ocular burning (31)	Hospitalization due to hypertension, angina, ear infection. (3) Hospitalization due to ocular inflammation (4) Death (2)	~52

Indacaterol study sponsored by Novartis

Indacaterol is an ultra-long acting beta agonist bronchodilator prescribed for chronic obstructive pulmonary disease (COPD) symptoms. Its trade name is Arcapta Neohaler. A 26-week safety and tolerability study of indacaterol in patients with COPD was conducted in India and the United States with identical protocols (16). It was a Phase II safety or efficacy study that was a multicenter, randomized, double-blind, double dummy, placebo-controlled, and parallel group study that used Formoterol and Tiotropium as active controls (17). The study consisted of two stages:

(1) Stage 1 of the study was designed to provide data about the risk-benefit of four dose regimens of indacaterol (75, 150, 300 and 600 µg) in order to move forward into Stage 2.

(2) Stage 2 provided pivotal confirmation on the safety of the selected indacaterol doses in patients with COPD. Among the four doses, Indacaterol (150 and 300 µg) were continued to Stage 2. The drug was continued to Phase III, as it was considered to be safe without any SAEs. The study entitled, “Safety, tolerability and efficacy of indacaterol in patients with moderate to severe chronic obstructive pulmonary disease (COPD)” was designed to evaluate the safety, tolerability and efficacy of indacaterol for 1 year compared to placebo in the treatment of COPD patients (18). It was a Phase III, multicenter, double-blind, placebo-controlled study that assessed the safety of two doses of indacaterol (150 & 300 µg) in patients with COPD.

For the Phase II study conducted in the United States, there were less AEs compared to placebo. These AEs included headache, muscle spasms, and upper respiratory tract infections there were very few SAEs. In this randomized phase II 42-patient trial, the results showed that participants with intermittent or mild to moderate persistent asthma, who received once daily dosages of the drug, had “effective 24-hour bronchodilation” compared to those receiving placebo (19). Results from the Phase II study conducted in India also showed that this drug was safe for patients with COPD and asthma, so the drug moved into Phase III studies in both countries.

For the Phase III study in the United States, the reported AEs were minor, and included diarrhea, nausea, and bronchitis. The number of AEs was very low in the treatment arm compared to placebo. The placebo arm had many AEs and SAEs, such as bronchitis, nasopharyngitis, sinusitis, and lower respiratory tract infections (20). After evaluation of the risk-benefit ratio of indacaterol in patients with COPD, it was launched in the United States (21). Although an identical protocol was used for the Phase III study conducted in India, the overall

incidence of AEs was similar for the indacaterol (active treatment) and placebo groups. The most common AEs in Indian patients were nasopharyngitis, cough, upper respiratory tract infection, headache, and asthma. The most notable AE, which may clearly have influenced treatment compliance, was post-inhalation cough, which was found in 53% of the patients. The number of patients who reported SAEs for indacaterol at a dosage of 300 µg was more than the placebo group, these SAEs included angina pectoris, myocardial infarction, and sick sinus syndrome (22) (See Table 4).

TABLE 4: AE data for indacaterol from the United States and India.

S.No	Country	AEs	SAEs	Number of patients enrolled in Phase III trial
1.	United States	Diarrhea (12) Nausea (14) Bronchitis (2) Sinusitis (6)	None	207
2.	India	Post inhalation cough (13) Nasopharyngitis (17) Upper respiratory tract infection (21) Head ache (29) Eye pain (17) Wheezing (37) Cough (27) Asthma (12)	Angina pectoris (7) Myocardial infarction (5) Sick sinus syndrome (18)	208

Discussion

One explanation of the eruption of outsourced clinical trials to India is that many major drug manufacturers in the United States and Europe have partnered with leading India-based Contract Research Organizations and hospitals. However, of late, there have been alarming reports in India of huge numbers of patients in clinical trials experiencing SAEs that lead to hospitalization (28). Many reports have also introduced the issue of unethical conduct affecting subject safety. It is evident that India's large population and versatile service sector offers huge opportunities for growth in drug manufacturing and clinical drug testing (23). However, the increase in recent AEs from clinical trials has proven to be a serious obstacle for biopharmaceutical and pharmaceutical industries. In January 2013, India's Supreme Court delved into the issue of unethical clinical trial conduct and negligence of pharmaceutical companies (24). The Central Drugs Standard Control Organization estimated that approximately 1 in 50,000 people are enrolled in clinical trials in India, and between 2009 and 2012, about 352,475 deaths were reported (25). In February 2012, non-governmental organizations filed a public interest lawsuit to bring to light the incidents that occurred in Andhra Pradesh and Gujarat, where 25,000 girls were administered a vaccine without following proper informed consent procedures (26). A review also highlighted the involvement of major pharmaceutical companies in the death of 438 patients in 2011. The report also stated that the drug companies defended their involvement by giving compensation to the families in the amount of 1.5 lakhs (\$3000), although after carefully reviewing the data, it was found that compensation was paid to only 22 patients out of 438 patients (27).

All of these severe events underscore the importance of patient safety during the conduct of a clinical trial. One example of how the quality of safety data is affected due to poor training

of clinical trial operations and training is the ixekizumab trial, which was a multi-center study consisting of 142 patients from United States and 125 patients from India, who had moderate to severe psoriasis. Psoriasis is an autoimmune disease, which causes overactive skin cells to proliferate on the dermis. A patient suffering from psoriasis often experiences anxiety and social isolation, as this disease also affects the patient's quality of life. Therefore, patients should be treated with utmost care or they may experience social stigma, as this disease is differently understood in different countries. Therefore, it is clear that AEs experienced in clinical trials for a disease like psoriasis may be more alarming in certain regions due to factors like geography, patient population selected for the clinical trial, and patient ethnicity (29). Ixekizumab was tested in American and Indian patients with the same protocol constraints; however, the analyses of AE data obtained from the clinical trial confirmed that there was a greater number of AEs reported in India than in the United States. It was also evident that the AEs reported in United States were less severe, and did not damage the patients' quality of life. In India, the seriousness of the AEs was higher, and there were cases, such as peeling and scaling of the dermal layer, that affected the patients' quality of life (30). In this scenario it is evident that certain factors, like geographical location, condition of the patient, or disease prevalence, may have had a role to play in the AE's experienced by the Indian patients. However, there are other factors that should be focused on as well:

- Ixekizumab was administered to the affected area, however, was the drug efficiently administered to the affected area by the staff? If the staff are not well-educated on protocol requirements, AEs such as skin rash and skin aberrations, can occur.
- If the patient is experiencing any symptoms after drug administration, they should be able to immediately report it to the staff. Staff should also be trained on how to educate

patients, and how to report or record events in their diaries or through the provided means of documentation.

Other factors that could be of a concern are the storage facilities and handling, and the storing and collection of lab data at the clinical trial site. This can be illustrated using the Restasis study as an example. Restasis helps to treat dry eyes in patients suffering from ocular inflammation due to keratoconjunctivitis sicca. However, the safety of this drug is a concern, as of the 44 patients enrolled in the study in the United States, two SAEs were reported, and even more were reported in the 52 Indian patients. In addition, a death occurred in India that was thought to be related to the study procedure. Upon further investigation of the drug components and its effects, it was found that the formulation of cyclosporine releases impurities (cyclosporine C, cyclosporine B, cyclosporine, dihydrocyclosporine A, cyclosporine D and isocyclosporine A) when not stored in a proper environment (31). The effect of cyclosporine A is known to cause hepatotoxicity, nephrotoxicity, gingival hypertrophy, tremors and increased blood pressure. Cyclosporine B is known to cause convulsions and blurred vision. Cyclosporine C and D are known to cause effects such as pain in the upper stomach, loss of appetite, and uneven heartbeats. After researching the drug components and their properties (impurities), it became evident that these impurities may have resulted in the various AEs and death of the Indian subject. Thus, utmost importance should be given to drug storage conditions at clinical trial sites, as variations in conditions may alter their effectiveness and cause further safety concerns.

The safety and tolerability study of indacaterol is a distinct example of how factors like the prevalence of the disease, patient awareness on hygiene; patient illiteracy affects the incidence of serious adverse events during the clinical trial. The objective of this study was to provide data

about the risk-benefit of the prescribed doses of indacaterol (75, 150, 300, and 600 µg), along with confirmation of safety doses in patients with COPD. This drug was proven to be safe at doses of 150 and 300 µg, without any SAEs. Based on the results from the Phase II study, this drug was successfully moved forward to a Phase III “multicenter, double blind, placebo-controlled study (18)”, where many SAEs were reported, in India when compared to the United States. The major SAEs included angina pectoris, myocardial infarction, coughing, and sick sinus syndrome. However, the response to the drug was good in both countries, and the data obtained was helpful in determining the dose-limiting toxicity of the drug. After reviewing into the patient data, it was found that of the 415 patients enrolled in the trials in the United States and India, there were cases of patient unwillingness to take one dose of drug, patient unwillingness to report AE outcomes, and scenarios where subjects were re-educated several times on drug dose and maintenance of a patient diary. It is possible that the diverse nature of India, with respect to culture and language, may be the causative factors of such scenarios. Or the reason may be as simple as the patient reporting “unknown” on the case report form as it was found that a large portion of the patient pool enrolled in the study were illiterates. However, these scenarios can affect the course of data collection as well as data analysis (24).

On reviewing the drug trials of the drugs discussed in this study, along with reports from various studies published between 2009 and 2011 that describe the alarming rates of SAEs resulting in deaths indicate that there is indeed an imbalance in the system and in the conduct of clinical trials in India (25). The incidents in Andhra Pradesh, Gujarat, and Bhopal demonstrate that even major drug companies seem to consider the patient pool as guinea pigs for clinical trials. They also highlight the lack of an effective body that makes sure patients have given their consent, and determines whether a trial subject is part of a vulnerable population (33). Finally,

these incidents also draw attention to the fact that India is a demographically diversified and populous country, with the potential of being misjudged and exploited in the name of better medical facilities and therapeutic breakthroughs (34).

However the ultimate challenge remains the standardization of both local and regional regulations. Emphasizing on a body that assures subject's rights like the Institutional Review Board/Independent Ethics Committee is also important. In India, additional barriers like cultural barriers, linguistics, economic-growth, and literacy are challenging for a foreign sponsor to overcome. While these barriers are bridged through a sound ethical system and effective communication, the parameters that would help in the successful staging of a clinical trial in India are the ones that need to be focused on. Subjects who participate in clinical trials need to be made aware of the benefits and risks associated with treatment. We know that many studies collect data using several questionnaires. If these are in English, they need to be translated into the required dialect or language, and staff should make sure that the subject is educated in how to properly answer these questions. A panel could be set up wherein source documents written in the local language can be translated by a linguistic expert to ensure that the correct data is written on the case report form, and to ensure that the subject understands, and is aware of the AEs of the given drug and how to report them. In this way, issues of safety and the ethical conduct of clinical trials in India can be addressed (35).

Therefore, considering economic and demographic developments, it is evident that India is one of the emerging markets for clinical trials. There are numerous advantages to conducting clinical trials in India, including reduction in trial costs, the vast number of hospitals, the many treatment options, the large access to a diverse subject pool, and the prevalence of a variety of diseases (36). However, many occurrences of misconduct in clinical trials in India have been

reported (37, 38). Another important aspect is that clinical trials sponsors would always want to display on how well their drug responded on the Indian population in comparison to other counter parts in various countries. And so as a result of this demonstration the data with high frequencies of all the events between the two comparator countries may not be released or acknowledged for reasons of reputation. Therefore, it can be assumed that there may be even higher number of events gone unnoticed or neglected. Hence, a consistent effort should be made to analyze the safety profile and therapeutic area of the drug being tested. However, recommendations are offered to assure additional protection of Indian subjects.

Recommendations

The anomalies in the system can be addressed by giving a thought to implement the below recommended:

A suitable administrative body should be placed in charge of overseeing the progress of the clinical trial. It is essential that the quality of the study be checked at every interval of the clinical trial process. These are, however, tentative suggestions based upon currently available data. Due to the possible under-reporting of adverse events, there has been difficulty in procuring supporting information in India.

- Site feasibility studies: Every sponsor should conduct them. These studies would help in identifying potential sites with respect to their infrastructure, investigators, trained site personnel, and most importantly, potential subjects.
- In terms of the infrastructure of a potential site, the site should have the following basic amenities:

1. Laboratory facilities
2. Exclusive pharmacy and drug storage facilities
3. Source documentation storage/facilities
4. Administrative aspects: local guidelines and procedures for ethically conducting a clinical trial
5. IRB/IEC- EC should be an independent component

Conclusion

This study illustrates the review of the incidence of adverse events and serious adverse events that occurred during the drug trials with respect to ixekizumab, indacaterol and Restasis. It also provides an interesting perspective on how the conduct of the clinical trials can be affected due to factors like regulations, clinical operational training, clinical trial site management, diversified ethnicity, culture and illiterate population in a country like India. The results also portray, the under reporting of the adverse event data which could lead to loss to data quality and integrity during the data analysis. Therefore, it becomes essential for a sponsoring (Pharmaceutical/ Bio-pharmaceutical) company to understand these affecting factors and study them prior to the conduct of clinical trial in India.

This study however had a few limitations with respect to studying and identifying core pitfalls in the Indian system of clinical trial conduct (with respect to regulations). There may be more aspects to this type of review, provided more cases of events are discussed with elaborated examples. Already existing or presented data indicates the point that besides following similar structured protocols in both the countries people in India end up suffering from more adverse events when compared to the United States. Having said that there is broader scope to the study, more and more information needs to be procured to formidably support the claim.

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