

A RIGHT DIRECTION OF e-CLINICAL TRIALS IN HEALTH INDUSTRY THROUGH IT

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ABSTRACT

Objective: Clinical trial is an inextricable link between advances in medical research technology and improved health care. It is a component of medical health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness and promoting health, the present study investigated the facts of clinical trials and to highlight the features of e-clinical trials through information technology system.

Methodology: The study has been carried out using secondary data from different sources which includes official website of the clinical trial gov and published articles.

Results: Challenges encountered by the pharmaceutical industry in the research and development of clinical trial process include design of clinical trial, lack of epidemiological data in specific time, problems in assessing clinical relevance and cost-effectiveness, lack of knowledge and training, and high prices.

Conclusion: This paper puts forward certain suggestion in order to strengthen the e-clinical trials. Under the e-clinical trial process the pharmaceutical industry has to achieve a great success in development of clinical data in the patients of various diseases and has brought them a great relief.

Key words: e-clinical trials, Electronic Data Capture, Clinical Research Organization

Introduction

Clinical research is now considered one of the promising areas in the health care industry. This is one of the fastest growing disciplines in the pharmaceutical industry in India. According to the leading discovery reports, the global clinical trials industry is currently about \$ 10 billion and has the potential for fast growth in the future. The Indian clinical trial market has grown from \$ 35 million in 2002 to \$ 120 million in 2006. It is estimated that this market will grow to a larger extent by 2010. Center watch expects it to be around US \$250-300 million. ^[1] Whereas Mckinsey estimates a much higher figure of US \$ 1.0-1.5 billion. In 2002, 40-50 clinical trials were conducted by 200-250 investigators and presently we have 700-1000 investigators in India. In USA, 40,000 investigators are conducting about 60,000 trials. There is increase in number of clinical trials in specialized sectors. US companies are testing about 861 new cancer medicines and vaccines as per the report of Pharmaceutical Research and Manufacturers of America (PhRMA) published in April 2009. In India a large number of clinical trials are being conducted over the last few decades and the numbers of global clinical trials being conducted in India are on the rise (Table 1).

In the past, Latin America and Eastern European countries like Romania, Russia, Poland, the Czech Republic, Hungary, Slovenia, and Croatia were preferred over India for carrying out clinical trials, but recently India is being considered a global hub for these trials. Over the last 15 years, internet and e- technologies have become an integral part of everyday business in most sectors, but have taken time to gain traction in the clinical trials arena. As the industry faces unprecedented challenges and further consolidation, companies are increasingly embracing technology as a lever to differentiate themselves, boost productivity, and succeed in the new environment. This review focuses on the importance is to introduce about the basic steps of clinical trials and why they shifted from slow-clinical trial to e-clinical trials.

Table 1: Number of permissions granted by CDSCO for Conducting Global Clinical Trials in India.

Year	Permissions (approx.)
2005	100
2006	150
2007	250
2008	200

Clinical Trial

Trial is from the Anglo–French *trier*, meaning *to try*. Broadly, it refers to the action or process of putting something to a test or proof. *Clinical* is from *clinic*, from the French *cliniqu’e* and from the Greek *klinike*, and refers to the practice of caring for the sick at the bedside. Hence, narrowly, a *clinical trial* is the action or process of putting something to a test or proof at the bedside of the sick. However, broadly it refers to any testing done on human beings for the sake of determining the value of a treatment for the sick or for preventing disease or sickness.^[2]

A clinical trial is a research study in which a treatment or therapy is tested in people to observe whether it is safe and effective. The information obtained from clinical trials helps to improve health care and to keep people healthier.^[3] It is also conducted by researchers to find out which treatments are more effective than others. The results of clinical studies give better knowledge about diseases and its conditions. Clinical trials are also called medical research, research studies, or clinical studies. Each trial follows a protocol, a written detailed plan that explains why there is a need for the study, what it is intended to do and how it will be conducted. The protocol is written by the trial's principal investigator.

They aim to find the best ways to:

1. Prevent disease and reduce the number of people who become ill
2. Treat illness to improve survival or increase the number of people cured
3. Improve the quality of life for people living with illness, effects of other treatments,
Such as cancer chemotherapy
4. Diagnose diseases and health problems

Why clinical trials are important^[4]

Clinical trials are the best way to compare different approaches to preventing and treating illness and health problems. Health professionals and patients need the evidence from trials to know which treatments work best. Without trials, there is a risk that people could be given treatments which have no advantage, waste resources and might even be harmful. Many treatments that have common use in health care were tested in clinical trials. Some types of clinical trial are designed to look at a treatment at an early stage of its development. Researchers and regulators will look at the information they have gathered and decide whether it is safe and appropriate to continue the development of that treatment. If the treatment has no benefit or has serious side effects, it may not be developed further. During the later stages of development of a treatment researchers will report on the benefits and risks so that doctors can decide whether or how best to use it. It is important that the results of clinical trials are published so that others can use the information to help them make decisions about treatment and health care. Clinical trial results also form an important part of the evidence used to decide whether a particular treatment will be provided through the NHS.

How the Trials set up

Clinical trials are designed by doctors and other specialists with input from a wide variety of people, increasingly including patients. They work together to decide what questions need to be answered. First of all they look carefully at the results of the trials that have already been done to find out what is already known. This is called a systematic review. A systematic review provides more accurate answers than individual trials and also helps to identify important questions that still need to be answered through further research. Doctors, nurses, patients and researchers work together with statisticians, trial managers and representatives from pharmaceutical companies if relevant, to design the best possible trial. The design for the trial forms the basis of the trial protocol.

When the trial protocol is ready it is sent to a research ethics committee, an independent group of people that includes doctors, nurses, other medical staff, members of the public and sometimes lawyers. They decide whether the trial is ethical. In particular they check whether the potential benefits of a new treatment are likely to outweigh the side effects the information provided to help people to decide whether they want to participate in a trial is clear and satisfactory, the way in which people will be asked to take part in a trial (recruited) is appropriate. There will be

compensation for people in the trial in the unlikely event that something goes wrong, travel expenses will be offered to people who take part. The trial can only go ahead when it has been approved by an ethics committee. ^[5]

Problem faces during Clinical Trials

Recently clinical trials are facing lot of challenges. Firstly there is no common acceptance from experts upon the definition of clinical research. Secondly, an imperfect public understanding of clinical research, it means that a relatively small percentage of people who volunteer to participate in clinical research trials for example, for adult patients with cancer, the volunteer rate are only five percent. The third problem is that the data are inadequate to tell whether investment in clinical research is being well spent or not. Fourth problem is about the insufficient funding in certain areas of clinical trials. The fifth and sixth problem is related to work force issues involved in clinical trial. The seventh problem is poor coordination between Health Medical Officers and the academic medical centers, between schools of nursing and schools of medicine on the other. Eight problems are concerned with the financial risk for academic medical centers and their ability to sustain their systems for clinical research. The output of all challenges is that there is no clear and dynamic agenda for clinical research. ^[6]

There is a need to set up a clinical research task force to examine what the academic medical centers need to do to strengthen their clinical research programs. The task force should divide its role into four specific tasks: examining the current status of clinical research education in medical schools and teaching hospitals, describing the optimal infrastructure for the different categories of clinical research, addressing the organization & administration of clinical trials and exploring the interface of clinical research with evolving clinical delivery systems that are academically affiliated. So there is need of sophisticated work force for more clinical investigation, to carry better job of educating all practitioners about clinical research, to persuade students and residents to stimulate their interest in clinical research careers. In other words health system needs to bring more research into practice.

Basic points to consider in designing a clinical trial ^[7]

1. In case of conducting a global clinical trial, it is necessary to evaluate effects of ethnic factors specific to individual regions on efficacy and safety of the investigational drug in specific place.
2. It is necessary that designs and analytical methods for the global clinical trial should be acceptable to specific country.
3. The primary endpoints should be those acceptable to all individual regions. If the Primary endpoints are different by region; data on all the primary endpoints should be collected in all regions so that inter-regional difference can be examined.
4. To allow for appropriate safety evaluation, the collecting and assessing method of adverse event information should be standardized as much as possible across all regions

Basic requirements to conduct a clinical Trial ^[8]

1. The clinical trial can be conducted in compliance with the ICH-GCP in all participating countries and clinical trial sites, etc.
2. All the participating countries and clinical trial sites can accept GCP audit from specific country.
3. Along with prior consideration regarding factors (race, region, patient demographics, etc.). That may affect to the efficacy and safety of an investigational drug, subgroup analysis based on relevant factors can be possible to achieve and appropriate considerations should be provided.
4. Social differences such as customs, and practical situations such as control and management of clinical trials in each trial sites can be properly understood and appropriate considerations if the differences could affect to trial results can be provided.

Types of clinical trials ^[9]

Clinical trials are used to study many aspects of medical care:

- 2.1 *Treatment trials*: It involves test treatments for a specific disease, new combination of drugs or new approaches to surgery or radiation therapy.
- 2.2 *Supportive care trials (Quality-of-life trials)*: It explores ways to improve comfort and the quality of life for individuals with a chronic illness.
- 2.3 *Prevention trials*: It looks for better way to prevent disease in people who have never had the disease or to prevent a disease from returning
- 2.4 *Screening trials*: It includes the study of new ways of finding diseases or conditions in people who are at risk, before they have any signs or symptoms.
- 2.5 *Diagnostic trials*: These are conducted to find better tests or procedures for diagnosing a particular disease or conditions.

Phases of a clinical trial ^[10]

Clinical trials take place in phases. The trials at each phase have a different purpose as the therapy will be tested in people. Before a clinical trial can start, there is need to do preclinical studies, which include cell studies and animal studies.

Phases of a clinical trial are given below:

3.1 Phase I: It is the first stage of testing in human subjects. In this 20-80 groups of healthy volunteers will be selected. This phase includes trials designed to assess the pharmacovigilance, tolerability, pharmacokinetic and pharmacodynamics of a therapy. There are two specific kinds of Phase I trials-

SAD (Single Ascending Dose) studies in which a group of 3-6 patients receives a small dose of the drug and observed for a specific period of time. If no adverse effect was observed, a new group of patient is then given higher dose. This is continued until MTD (Maximum Tolerated Dose) is shown.

MAD (Multiple Ascending Dose) studies in which a group of patient receives a low dose of drug then dose is subsequently escalated and sample is collected at various times. It is conducted for better understanding of the pharmacokinetic and pharmacodynamics of the drug.

3.2 Phase II: This phase shifts the focus of trials from safety to efficacy and is performed on large groups of 100-300 individuals. Side effects from new drug product are also investigated; the development process for a new drug commonly fails during this phase due to poor efficacy or toxic effects. Studies are divided sometimes into Phase IIA (to assess dosing requirement) and Phase-IIB (to study efficacy).

3.3 Phase III: These are the longest most comprehensive, expensive and time consuming trial and design for chronic condition. These are controlled trial on large patient group (1000-2000 or more) and are used for assessment of the efficacy of new therapy, especially in comparison with current available alternatives. The compounds that successfully complete this phase have 95% chances of testing approved by the FDA.

3.4 Phase IV: It involves the post-launch safety surveillance and ongoing technical support of the drug. Studies may be mandated by regulatory authorities or may be undertaken by sponsoring company for competitive or other reasons. Post-launch safety surveillance is designed to detect any rare or long term adverse effect over a longer patient's population. Such adverse effects detected by this phase may result in the withdrawal or restriction of the drug (e. g Rofecoxib and Troglitazone).

How are trials supported?

Many of these organizations involve patients to help decide what will be researched in the future. It is essential that research takes into account the needs and interests of the people it is trying to help. Specialists are often aware of gaps in knowledge about many different types of organization support clinical trials, these include: the National Health Service, the Medical Research Council and government departments or agencies charities pharmaceutical companies. All trials, no matter who funds them, are checked and monitored in similar ways to make sure that the people who take part are protected. Each trial also has a sponsor who is responsible for the conduct of the trial. The sponsor may be the organization funding the trial or the institution hosting the research, for example, a university diagnosis and treatment but patients and their families may also see aspects of care that need further research.

Why paper based slow clinical trial is less useful than electronic clinical trials in the coming generations

Clinical testing of new drug candidates is an increasingly complex, lengthy and expensive process with a dauntingly expensive process tag. Companies developing pharmaceutical products face mounting pressure to increase the efficiency of the drug evaluation process, particularly in the clinical stages. Clinical departments are very expensive to run and maintain. They exist primarily to gain access to markets through product approvals. ^[11] The pharmaceutical marketplace is fiercely competitive and the demand for rapid access to approval new chemical entities is high, but the complexity and length of clinical trials, and therefore cost of development, continues to increase. Pharmaceutical companies and contract research organization (CROs) have recognized the need to increase the efficiency of the whole drug development process, particularly in the clinical phases, and technology initiatives have been heralded as the way to achieve these goals. ^[12] Earlier physician (principal investigators) adamantly opposed to the adoption of technology for data collection. Regulatory bodies were reluctant to accept crucial information in unfamiliar forms and non-traditional formats. When found lacking, the process of adjudicating inconsistencies or correcting inaccuracies was impossibly slow and fraught with systematic errors. When electronic clinical trial came into existence there was very little impact on the query result ions, patient recruitment, and reduction of time and trial process management. So in clinical arena, a non-profit, independent and international organization health levels HL7 was born. Their vision was to create a technology process whereby, clinical data

could be efficiently and securely transferred among providers and other critical users. So electronic clinical trial was defined as those clinical trial in which primarily electronic processes are used to plan, collect (acquire), access, exchange and archive data required for the conduct, management, analysis and reporting of the trial.^[13]

Every now and then, a shift in technology revolutionizes an entire industry. Consider the advent of email and automatic banking machines. Once the mainstream adopts these processes, it is difficult to imagine how we managed without them. Today a similar transformation is taking place in the pharmaceutical world, as more companies worldwide replace paper diaries with electronic patient diaries in clinical research.

As we enter 21st century, internet-based data collection, retrieval, and management are becoming the norm in drug and device clinical research. By increasing data quality as well as reducing the time to database lock, companies can reduce both times to market and development costs.

The process of converting from paper to Web-based clinical trial involves many stakeholders, including sponsors, independent clinical study sites, Site Maintenance Organizations (SMOs), Contract Research Organizations (CROs), and the regulatory authorities. But in our experience as a CRO, the greatest challenge to the implementation of Web-based trials lies within the sponsor company's organization.

The use of the internet is growing rapidly in the medical field as is demonstrated by the increasing number of medical journals accessible on the internet and the broadening access to medical information and organization on the internet. The internet and the world wide web have recently been introduced into the management of some aspects of large-scale clinical trials such as dissemination of information on trial progress, randomization and monitoring process, and remote data entry.^[14]

The past couple of years have seen an explosion of interest in the use of the Internet to conduct clinical trials of new pharmaceutical products. At the last count, over 60 companies supplied software or services using the Internet to some degree. Invariably the supplier's aim is to dramatically reduce the time required to bring a new drug to market. These claims probably sound familiar and many readers will remember the same claims being made when various forms of remote data entry and clinical trial software were introduced a decade ago. Experience, however, has taught us that none of these approaches consistently and significantly alters the clinical development cycle time; indeed, many suffered from difficulties that actually slowed the process down and proved very expensive.

Current approaches

Over recent years, there has been growing interest in the use of the Internet in clinical research. Firstly, Remote Data Entries (RDE), then Electronic Data Capture (EDC) and now clinical data warehousing have been positioned as the solution to reduce the length of the development cycle and gain early access to the market in order to regain investment in R&D. However, companies often do not establish upfront clear business objectives and key performance indicators against which to measure the success of their EDC implementation, which results in studies being perceived to be expensive or failures.

There are currently at least 60 companies who supply clinical trial software or services to the pharmaceutical industry, each of which use the Internet, to a greater or lesser degree, either online or offline.

Offline systems require the application to be stored and maintained at each trial site so that there are a number of local databases that need to be supported and ultimately integrated. The advantage is that the user does not have to be online while entering data but he/she does need to be prompted to download and back up data regularly.

Online systems do not require software maintenance at site and allow shared access to a single database. The disadvantage is that users need to remain online for the duration of their data entry (this may not be practical in areas where Internet connectivity is unstable or expensive).

Other technologies currently in use include Interactive Voice Response Systems (IVRS), Electronic Spirometry and Electrocardiogram (ECG) solutions, wireless applications, personal digital assistants (PDAs), imaging technology, electronic patient diaries that carry promises of enhanced patient compliance and just-in-time supply of medicines that are expensive or difficult to scale up. The limitation of these products is that they tend to focus on data acquisition alone and not what is done with the data once it is in-house.

Many pharmaceutical companies have run pilot programmes with several competing products but the pharmaceutical industry still lags behind other manufacturing industries, such as the aeronautical and automotive industries, in its adoption of technology initiatives. A recent survey of EDC-use found that 64% of respondents have in the past used.^[15]

Clinical data management and data quality are key strategic assets of large pharmaceutical companies and clinical research organizations that conduct human clinical trials. Data must be of the highest possible quality to meet both the requirements of accuracy in human trials and historically strict government regulatory conditions.

The complexity of data management continues to grow as both technological and business models for conducting clinical trials evolve to meet the demands of large, multicenter trials. In recent years, companies have begun to shift data acquisition from the traditional paper to electronic means. Electronic technologies now enable pharmaceutical companies and CROs to expand clinical trial data management and integrate far-flung data centers around the world. With this shift, the role of data management is more important than ever, even as the fundamental nature of clinical capture and database management has begun to change. Clinical trials today can be expensive, time consuming, and ongoing. Clinical data management is one of the fundamental, and often under appreciated, processes that control both data accuracy and timelines of every trial. Clinical data management links clinical research coordinators-who monitor all patient sites and collect all data-with biostatisticians-that analyze, interpret, and report data in clinically meaningful findings. In this sense, data management departments are much like commodity producers. First they harvest and refine raw clinical data. Then they package it in the form of databases for analysis by biostatisticians. All the while, they ensure its quality and accuracy for regulatory agencies.

Global data management groups comprise experienced, dedicated professionals who help oversee both traditional paper trials and e-clinical trials. Data Management teams have the requisite experience to manage programs in any phase and of any complexity, including large-scale Phase IV trials and expanded-access programs generating data from thousands of patients. Because each clinical trial is unique, data management groups typically first consult on strategies, systems, databases, processes, procedures, and metrics, including:

- 1 Database design, implementation, and validation.
- 2 Data capture, entry, validation, cleaning, and review.
- 3 Medical coding using standard dictionaries and thesauruses, including COSART, WHO, MedDRA, and proprietary systems
- 4 Safety procedures, including SAE reconciliation and management of protocol violations, deviations, and endpoints.
- 5 Quality assurances to client-specified levels.
- 6 Data consolidation, migration, and conversion.

Conclusion

Web-enabled clinical trial technology is undoubtedly changing the way that drug development is performed. The success will come to the organizations that maximize the benefits that new technologies can bring, the integrating technology into new business process and the working environment and most importantly, achieving the buy-in and support among its employees and external customers. In the future, the internet and clinical trial websites could transform that way a clinical trial is conducted; however, in order to achieve this goal each participating center must have adequate access to the internet. At that point, clinical data capture through the internet will be widespread and electronic mail will be commonly used and integrated with new tools such as videoconferencing and telephone on the internet thus improving interactive communication among all those involved in a trial.

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Conflict of Interest Statement

There are no conflicts of interest.

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