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SUBJECT RECRUITMENT CHALLENGES IN PHARMA AND CLINICAL RESEARCH ORGANISATIONS: A GLOBAL PERSPECTIVE

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ABSTRACT:

Subject recruitment is the dialogue that takes place between an investigator and potential subject prior to informed consent process initiation. It begins with the identification of research volunteers, targeting and enlistment of subjects (volunteers or subjects or controls) for a clinical research study. It includes giving information to the potential subjects and generating interest in the proposed trial or study. Problems with recruitment can disrupt the schedule for a research project, preoccupy staff, reduce the ability of a therapeutic study to detect treatment differences and, ultimately, result in a trial. Two main goals of recruitment include: To recruit a sample that sufficiently represents the target population, to recruit adequate number of subjects to meet the sample size and power requirements.There are potential drawbacks in the identification and recruitment of suitable candidates for phase 1trials and bioequivalence/bioavailability (BA/BE) research. The challenges of recruitment are highlighted, detailing impact of study design, subject characteristics, including demographics and personal preferences, investigator characteristics and collaboration with clinicians. Recruitment techniques are discussed, including financial incentives, assertive tracking and communication methods. The demand for healthy subjects for phase 1 and equivalence trial continues to increase. There are more trials including phase 1, bioequivalence trials, bioavailability studies being done, government regulators require an increasing amount of data and some within industry have noticed that subjects are becoming less willing to participate. These pressures have led to the development of variety of strategies to make the subject recruitment process more efficient and effective such as:the creation of research networks/linkages,the implementation of software to determine subject's eligibility and the use of email and the internet to find new subjects. Indeed, subject recruitment has become an industry. Competitive enrolment has emerged as one of the most important subject recruitment practices. Despite being worldwide, there is less literature on the nature and ethical implications of competitive enrolment. Competitive enrolment creates significant ethical challenges that need to be implemented by both regulatory and ethics board, at the level of national research ethics policy and regulatory authorities. Competitive enrolment is often part of the trial agreement between the research investigators and the sponsor of the trial. The goal is the advancement of subject recruitment rapidly.This research paper summarizes the collective research to avoid the problems faced by pharmaceutical and clinical research organizations in the subject recruitment. Aim of this research paper is to provide a balanced and objective approach to this research. Research focus on industry-sponsored trial due to recent years the clinical research environment has become more commercialized and competitive, as sponsors have assumed a more prominent role in the search for new drugs. In this changing environment, the quest to find healthy human subjects has rapidly intensified.

Sponsors and investigators are facing difficulty in finding enough healthy subjects in a timely manner to bring drugs to market within their desired time-frame.

KEYWORDS: *Subject;Recruitment;Challenges;Pharmaceutical;Pharmaorganisations;CRO;Clinicalresearch organisation; global; perspective;*

I. INTRODUCTION

Subject recruitment plays a major role in clinical trials for faster conduct of trials. As with the recruitment strategies, competitive enrolment schemes could create ethical challenges. Due to the goal of rapid registration, these strategies may compromise the informed consent process or cause investigators to put subtle pressure on subjects to participate. Subject drive to become a research participant is perishable and there is a need to create memo for every campaign of subject recruitment.Considering subject motivation as perishable and recruitment as a campaign is hardly consistent with the reflective, ongoing, no pressure, atmosphere that is meant to accompany the informed consent process(1). Given the pressures inherent in a competitive enrolment procedure, there seems to be a query that they challenge the investigator's requests to the subject that is, the request to check for the interests of the subject remain paramount. A competitive enrolment scheme is designed to place other objectives, the subject recruitment, and high on the investigator's agenda. At a minimum, legal duties intensify investigators request to conflicting interests. Competitive enrolment may also involve investigators to push the boundaries of a protocol's inclusion and exclusion criteria. This research paper considers strategies and tactics that enhance clinical studies efficacy and efficient by ensuring that appropriate subjects enrol in clinical studies in the most cost-effective manner. Clinical researchers also make subject participation attractive to avoid drop- outs, by giving various benefits and time lost from employments. Moreover, the clinical trial ethics go beyond the need for well-performed informed consent procedures. Ethics and politics are involved in the framework in which clinical trials are carried out in organizational features as well(1).

Research focuses on industry-sponsored studies in recent years the clinical research setting has become more competitiveand commercialized (7), as sponsors have presumed a more prominent role in the search for new drugs. There are potential pitfalls in identification and recruitment of healthy human volunteers for bioequivalence/bioavailability research and phase trials. The challenges of recruitment are emphasised, detailing impact of study design, subject characteristics, including demographics and personal preferences, investigator characteristics and collaboration with clinicians. Recruitment techniques including financial Incentives, assertive tracking and communication methods plays a significant role(4)".

CURRENT METHODS OF SUBJECT RECRUITMENT

Good recruitment practices

Successful recruitment, compliance, and retention will be achieved byGRP principles in the clinical study process (2). At first glimpse, it appears rational to think that subject recruitment and retention is nothing but a set of procedures in the linear process of progressing a subject starting from inquiry to completion, example. At the research site level. Motivated subjects are effectively selected for the period of the study (3). GRP aims to:

- Prepare subjects to attain at informed decisions about study participation.
- Improve the involvement of study participation for volunteers and clinical research physicians.
- Foster clinical research knowledge and education.
- Develop communication among all subjects involved in the clinical research and development process.
- Help ethical behaviour and decision-making in potential conflicts of interest.
- Reduces time and costs among the development of new drugs and other treatments.

- Provides guidance to investigators, sponsors, coordinators and study research site staffs, clinical research physicians, recruitment agencies and institutional review boards (IRB) through an organized set of principles(3)".

Standard categories among procedures include:

- Subjectdata and communications.
- Clinical study set-up, design, and conduct.
- Investigator-relating research physician relations.
- Subject incentives.
- Subject financial disclosures.
- Public knowledge and education (3).

SUBJECT RECRUITMENT STRATEGY BY SOLICITING INFORMED CONSENT

Clinical trials aresignificant step towards accomplishmentof drugs to market. U.S. based clinical trial activities improved by 6% in 2001, the largest increase since 1990. But pharma companies give attention to research when designing their clinical trials, considering sufficient subjectsto participate(5). As a result, most clinical trials are affected by delays that involve heavy costs pharma companies millions of missed sales. Delays in obtaining drug to market are coming around $1 million a day. Given that, on average, 40% of pharma companies R&D costs are reserved to clinical studies, and R&D expense is increasing by 10% per year, companies cannotafford such a situation (12).During the 1990's, the deaths of two healthy volunteers in US made their way to the highest political levels and forced a review of human subject's protections (11). Must audit the research site to ensure the regulatory requirements.

EU's group of research experts in clinical research on ethics have been showing on the challenges of conducting studiesin poor countries, the European clinical studies community has been showing on another important case—the needs of the growing elderly population in Europe (6). The European Forum for Good Clinical Practice meeting in Brussels is to enhance thinking on how to cope up this great minority. The challenge here is like the one the EU is trying to enhance research systems which promotes studies for subject recruitment(8). There is not enough space to report on first European move in area of debate—but it is vital to merit some extended coverage (6).

DATA BASE MANAGEMENT SYSTEMS - CORE DATA ELEMENTS

Undertaking Electronica Data Capture (EDC)/ eClinical technologies affords industries the chance to involve in process re-engineering for utmost effectiveness and return on investment. In short, these technologies change the timing and work flow.Siebel clinical trial/ study management system(Oracle's) gives a new and innovative method in managing clinical studies. This method focuses on building relationships with study participants, especially investigators by using customer relationship management (CRM) software tools (15).

DATA BASE MANAGEMENT SYSTEMS

A data base has been initiated which has the following elements:

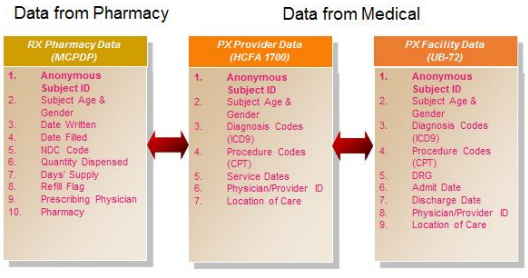

Fig.1 ***Database management systems (4) (7)***

The procedure has been applied in few research studies.Transparency occupies one and all mind. The World Health Organization (WHO) recently decided standards for registration of human medical research (9). WHO has requestedthe institutions and industries to record all research studies including the recent studies involving subjects or volunteers (3).Instead of acting as a register, the international clinical studies Registry Platform will perform standardization of all registries. By registering trials from the outset, findings, WHO hopes to make clinical research transparent and improve public trust. The registry will start a web-based research platform which will allow everyone to find among participating registers for clinical trials. The ideal response to recruitment problems is to include more research sites. The definition of irrationality is doing the same thing repeatedly, however expecting the different results.

Factors affecting subject registration in today's clinical trial world

- Informed consent
- Security
- Qualitative data collection (3)

Hurdles to recruitment and retention

Subject-related hurdles

- Trial participation additional demands
- Informed consent processes
- Subject's attitude towards clinical trials
- Subject's attitude towards study design
- Attitude of family members/ trial participants
- Impact of the investigator recruiting trial subjects
- Special dynamics of the subject (3)

Investigator-related hurdles

Logistical factors

- Lack of time
- Lack of rescues and training for the recruiters
- Unstable research team/ change in research monitoring unit
- Overestimation of available study population

Personal factors

- Subject concerns during the trial conduct
- Obtaining informed consent
- Investigator–subject relationship
- Clinical autonomy loss concerns
- Conflicting role dealing incapability
- Lack of interest in the research question (4)

Protocol-related hurdles

- Study or trial design
- Data collection requirements
- Inclusion and exclusion criteria
- Protocol procedures incapability
- Protocol disagreement by clinical investigators
- Investigator's lack of support and enthusiasm for the trial(3)

Other hurdles

- Negative influence of media.

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- Clinical research study depends on the subject care taken by study personnel's.
- Reimbursement methodology and subject retention strategies.
- It is imperative that study subject acknowledges the commitment and tasks required for participation.
- Trial drop outs are due to: misperceptions about clinical studies, protocol worries, protocol complexity, lack of motivation and lack of support, guidance during the study.
- Subjects who stick to study regimen are those who know about the trial and the condition, regimen aids for transportation arrangements.
- Commitment enhanced by community within the research study.
- Trial participant appreciations to be given throughout the study, including incentives.
- Study coordinators and principal investigators (PIs) also need proper research training.

Subject retention is the key to the clinical trial process. Not only during the investigator meeting there is a requirement ofupdate on inclusion and exclusion criteria and adverse event (AE) reporting, but PI also needs to elaborate on how to treat study subjects as customers rather than merely research subjects. Research site staff need to know what methods there for recruitment are, as well as the targets, objectives, time limits, and projected results for the study. Subjects deserve separate attention from everyone in the research site. Subject retention tools such as newsletters, postcards for appointments, appreciation things are delivered throughout the study, and follow-up phone calls are vital in making individuals make comfortable that they are integral part of study. These tools also teach subjects about their condition. Web-based information systems are now developed to assist research sites and pharma companies in subject recruitment and tracking analysis. Research site staff can also retrieve graphs pertaining to registration and subject outcomes for their research site. As subject information is updated, research site staff, sponsors, and clinical research organizations can have constant, real-time access to recruitment analysis plan using HIPAA-Health Insurance portability and accountability act compliant platforms (10). Flexibility is key in effective subject recruitment. It is vital to make it easy for subjects to stay with the study program (2).

CURRENT CHALLENGES IN RECRUITMENT OF RESEARCH SUBJECTS

Pharma companies and clinical research organizations are organizing and building upcumulative number of clinical trials worldwide. Thisbids more opportunities for sponsors to kindle subject recruitment and to carry out clinical trials according to international standards and regulations. Recent uncertainties about data quality and cost-reasonableness at investigational research sites, have led to regular research analysis ofclinical research sites capacity. It's important to introduce benchmarking and evaluation of performancefor thetrial conduct to identify best practices and to continually improve clinical research (4).

- Operational delays in clinical trials reduces patent response time and shorten productive phase of product's life cycle (PLC). The main source of delays is the recruitment & retention of subjects that fit the trial requirements.
- More drugs on trial have been formulated to attack specific targets. This necessitates the need to identify, recruit and retain subjects that fit a narrower medical profile (16).
- Pharma companies and clinical research organizations are finding ways to regulate recruiting operations and gain advantages.
- Subject Recruitment in clinical trials are aiming on successful approaches and emerging trends from across the globe.
- Volunteer recruitment means attracting and inviting people to consider involvement with organization.
- Many new volunteer administrators make the mistake of beginning their recruiting before they have an idea of why they are recruiting and for what positions.

- The most important step for recruitment is planning and design. To do this, we must spend time learning about regulatory issues in India & worldwide from the inside as well as how we have perceived by the community and public at large.
- Most critical success factors in clinical research is motivating subjects to participate in the clinical studies.

CLASSIFICATION OF PROBLEMS

- In identifying volunteers with previous history of illnesses
- Recruiting special population
- Recruiting illiterate volunteers
- Retainment of volunteers
- Web based volunteer recruitment
- Volunteer identification & database management
- Volunteers who had previously participated in any other research study
- Follow up of standard procedures/ guidelines / regulations (14)

CAUSES FOR THE PROBLEMS

- No standard system for volunteer identification & volunteer database management in India
- Volunteers who had previously participated in any other Study
- Clinical study personnel responsibilities
- CROs doesn't follow standard procedures/ quality systems for conduct of BE/BA Studies
- Regulatory & ethical Issues

PREVENTION OF PROBLEMS

- Informed consent: volunteers who had previously participated in any other study
- Proper data base with subject names & identification codes
- Regulatory issues
- CROs must follow Standard procedures/ guidelines / regulations/ quality systems for conduct of BE/BA Studies to avoid volunteer participation
- RA-Standard System should be introduced for volunteer identification & Volunteer database management (Sharing of Information's across CROs)
- Ethics Committee must audit the site
- Responsibilities of Principal/ clinical investigators/ CRAs / CRCs / VMOs / Volunteer recruiting Organizations
- Applications of data management techniques (17)

APPLICATION OF TECHNIQUES IN REDUCTION OF PROBLEMS

- Biometrics-special identification methodology
- Sharing of information across CROs-volunteer data bases
- Data base management techniques- SQL Data bases, VB
- Smart card system (should be upgraded)
- Registries

Regulatory ethics board must recognize subject enrolment is an upcoming ethical concern. It is a practice that involves ethical issues as unequal physician reward and recruitment incentives, methods that are generally not allowed by research ethics policies. Regulatory ethics board and research investigators have a request to treat and if, contractual requests generate inappropriate conflict of interest matters. The real meaning is that regulatory ethics board must thrust the submission of agreements between research investigators and sponsors.

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REGULATORY & ETHICS BOARD MUST:

- Develop data flow and exchange methodology first and software design solution to fit the model if commercial tool development is not possible.
- Identify and use recognisedrescues to contribute hardware and software costs. Partnership with a clinical research centre if available.
- Consult IRB and HIPAA experts early in early project development stage.
- Check for confirmation and data security procedures are in place at all stages of project development.
- Develop clear policies for registry use by research investigators.
- Balance the need to keep registrant data entry as simple as possible with the goal of collecting sufficient information to allow clinical researchers to pre-screen subjects most likely for participation to be qualified.
- Make the system robust and autonomous and self-sustaining as much as possible.
- Instruct clinical personnel and operators to engage potential volunteers who query about research studies to use the registry.

RECOMMENDATIONS

Effective healthy human volunteer recruitment programs have become more critical to industry. Nearly 10 % of eligible healthy human volunteers taking part in clinical trials at any time, healthy human volunteer recruitment programs can increase sponsor's capability to reach those who have never considered taking part in clinical research.

1. From time to time, there are explanations not to share data. They include failure to secure informed consent from study volunteers and need for research scientists to first publish findings.
2. Data sharing depends on assuming robust acquisition and recordkeeping. Data acquisition and record keeping is a potential feature of clinical research and technology. It provides the basic information on subsequent data analysis and classifications. Without proper data collection and record keeping, subsequent data use has been treated as questionable authenticity and accountability. Record keeping have been considered as vital importance for patentable inventions. Objectivity is basic principle of research investigation. It will not be easy, even for people with best knowledge, to acquire, process, and report data not in biased way, but that is goal to which research scientists aspire. Skill at avoiding bias comes with practice, but depends mainly on knowing the goal, carefully thinking how to achieve it.
3. It is intended to providecurrent thinking in the academic community and the regulations developed by number of institutions, agencies and professional organizations who had spent considerable time in analysing the issue and offering broad range of principles and issues to consider.
4. A skilful collaboration of both marketing and management perception together with clinical research expertise makes recruitment campaign sing.
5. Responsibilities lies in research volunteers & recruitment personnel's

- Must check for whether volunteers had previously participated in any other study
- Must follow regulatory standard procedures/ guidelines
- In obtaining informed consent

The ethics board must analyse clinical studies to help clinical researchers in avoiding conflicts of interest concerning the recruitment of subjects and rewards by sponsors to the clinical researchers. To complete this task, it has been advised that boards will have to create some expertise in assessing financial arrangements. Regulatory ethics board should ask to sensitize research investigators about enrolment agreements are formed to create incentives which compromises the investigator's ethical requests. This is necessary for inexperienced investigators who may practice in the community. Regulatory ethics board wants to consider compelling the disclosure of competitive enrolment agreements to subjects as part of the informed consent method. Research investigators are needed to show information about differences (13).

It involves showing of competitive recruitment scheme and extended same research ethics policy. It is certainly debatable that this is part of the research investigators informed consent request as it is something that in the subject's position would like to know. Legal principles require clinical research physicians to disclose information about factors that may compromise their involvement to the interests of research subjects. Finally, on a wider scale, the issues associated with recruitment needs national attention. As with inappropriately generous physician incentives and non-disclosure agreements, it is not easy for regulatory & ethics board to act on their own without guidance at the level of national policy – this is especially so when a practice is a standard approach

Improving volunteer recruitment procedure in the future

- Responsibilities lies in the hand of Recruitment personnel's
- Volunteer responsibilities
- Data bases (SQL, VB, Oracles Siebel) with subject names & identification codes
- Regulatory & Ethical Issues
- Must Introduce Registries
- Standard Systems (Health card system) should be introduced for volunteer identification & Volunteer database management (Sharing of information's across CROs)

Newer approaches to enrol subjects and expedite clinical trial:

- Achieving realistic recruitment rates
- Understanding the Principal Investigator/ Clinical Investigator's role
- Experimenting with recruitment options
- Protocol review
- Aid
- Communication
- Getting the message across
- Using technology
- Increasing public confidence in studies
- Informed consent vs informed decisions

This research will help to understand the various factors affecting pharma and CROs worldwide in subject recruitment considering recruitment in U.S., Europe, Japan & India. It also identifies successful strategies to combat the clinical studies productivity crisis for faster and smoother recruitment.

II. CONCLUSION

Regulatory authorities must inspect key recruiting trends across the U.S, Europe and Asia to understand the evolving problems faced during the subject recruitment and retention. Pharma companies and CROs should investigate and benefit from database-real world recruiting techniques that offer untapped potential to recruit both subjects and clinical research physicians. Recruiters must stay up to date with recruitment strategies for subject and physician recruiting initiatives and identify what can be incorporated into clinical objectives. Regulatory authorities must integrate new recruiting strategies into clinical programs and reduce drug discovery delays. Organisations must assess the applicability of different recruiting strategies to clinical development programs.

We need sound science, ethics and safety in volunteer recruitment to sustain the trust of sponsors, governments, public and specifically, research subjects to allow research for the advancement of medicine. Hoping to implement standard systems in place globally to avoid subject recruitment challenges

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