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WHITE PAPER

Patient Search in Clinical Trials – history, current trends and technological advances.

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Abstract

A brief overview of historical development of the clinical industry and its effect on life expectancy of patients is given. The general trends of study sample site increase, reduced patient participations and challenges associated with patient recruitment and retention are reviewed. A case is made for replacing manual database scanning with IT infrastructure, resulting in quicker identification of eligible patients. Patient Recruitment System (PRS) developed by Clinerion is presented and its three main features (protocol authoring, feasibility and real-time recruitment) are reviewed. Implications of global implementation of PRS on site selection process and clinical trial management in general are discussed.

Patients in Clinical Trials

The increases in life expectancy and quality of life in the last century are emphasized in all health statistics. Although some authors point to an "increased female literacy rate" as the most important reason for this progress, the consensus suggests that clinical trial development is the most compelling reason (the impact rate is 40%). We would like to remark on the importance of clinical research, while accepting this exchange as an open discussion.

Clinical trials play a pivotal role in medical advances and in the drug development life cycle. It is quite possible to trace the beginning of clinical trial history to ancient times. Over the centuries, changes in scientific perspective have affected the doctrine of clinical research. Active participation by patients/human subjects in clinical research is one of the most critical factors driving successful drug development. Although preclinical laboratory research has been well defined through animal models, many regulations worldwide will not accept a drug's claim of health benefits without human subject experience. The competence of any clinical trial is bounded with many conditions, most importantly, sufficient volume and desired quality of patient data. Consequently, throughout history scientists and patients have developed an interdependent relationship.

Today, we see that research procedures are more sophisticated; for example, the required study sample size is increasing and the duration of the studies is often longer. However, patient recruitment and retention rates have declined steadily.

Patient Trends

With the development of evidence-based medicine, the evaluation of scientific publications is changing. Research designs are classified according to the evidence value; the sample size and the selection criteria of the subjects are more scrutinized. Comprehensive meta-analyses with the mission of identifying "universal truths" are more frequently published.

While these shifts help bring about a barrier to scientific fraud, the cost of proving added health benefits and/or improved outcomes with innovative drugs becomes much more challenging. In order to strengthen the evidence of the research, researchers need to study the drug's effects in a larger sample population.

A study conducted in Italy reveals that within six years, there were 65% more clinical trial applications and the average duration increased more than 70%; however, the patient participation rate reduced by 21% and the retention reduced by 30%.

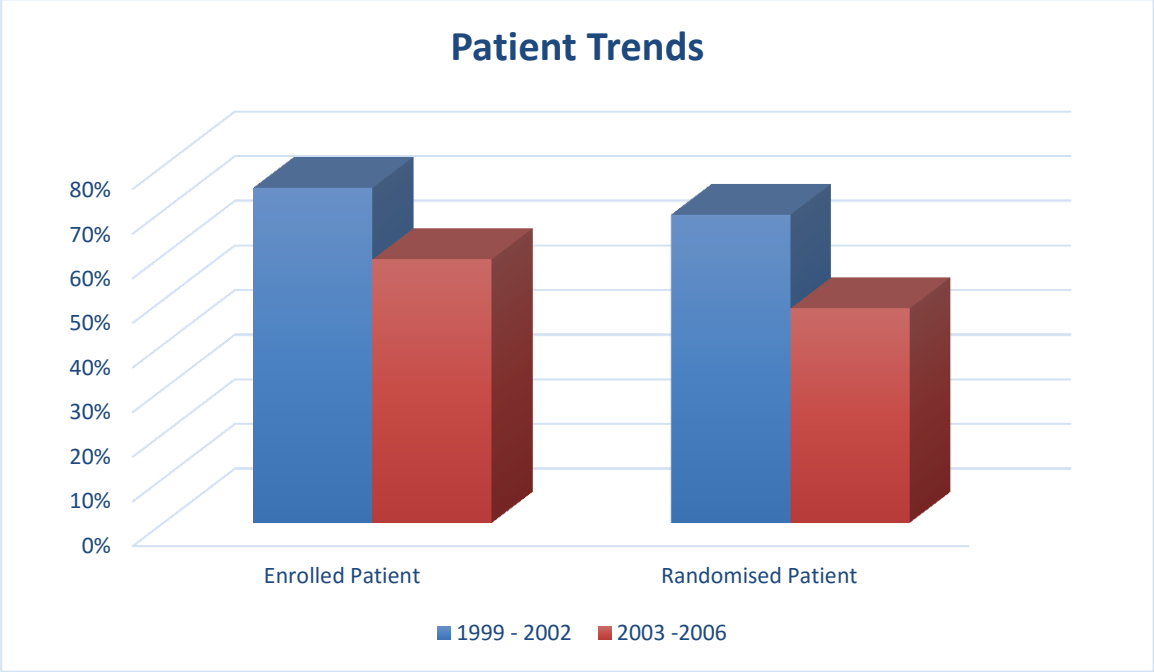

Fig. 1. Patient Trends. Ref: Sen A. "Clinical Trial Recruitment & Retention" (Published on September 23, 2013)

In another study, more than 80% of the international trials failed to reach a sufficient number of patients in the planned recruitment period. Indeed, 26.5% of investigator-initiated trials and 8.4% of sponsor-initiated trials faced early termination due to an insufficient number of patients. Even if the mentioned researchers published the evidence, its medical value would be considered as questionable.

Along with the above trends, the drug development costs have increased: in 1979 the cost of a drug was $100 million, in 2005 $1.3 billion, today it is over $1.7 billion.

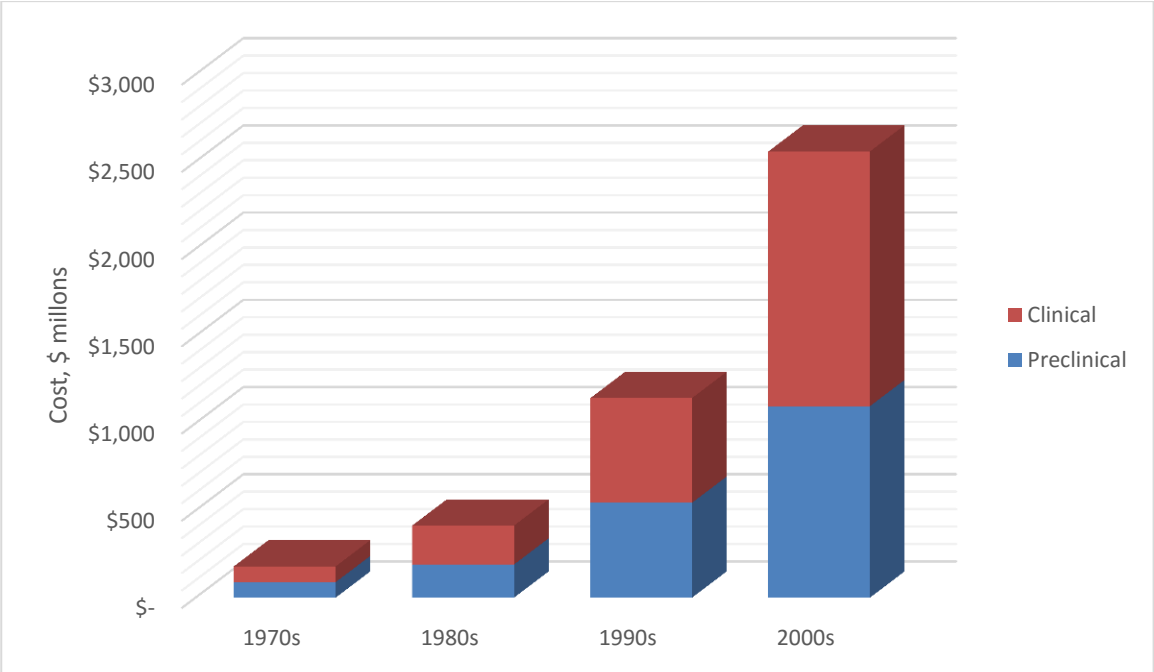

Fig. 2. Increase in drug development costs over the past 40 years. Ref: Tufts Center for the Study of Drug Development (Published on November 24, 2014)

Analysis of Trends

Today, our expectations of drug safety, understanding of benefits and risks, and regulations have increased remarkably compared to previous generations. Negative experiences, such as the thalidomide disaster in the early 1960s, show how drug development affects those at the community level. The necessity for more stringent regulations for the pharmaceutical industry has largely increased the cost of research and development activities.

The challenges facing clinical trials are not only growing costs (thereby increasing risk), they are also threatened by falling patient participation and retention trends. An insufficient number of patients will generally reduce the reliability of clinical research.

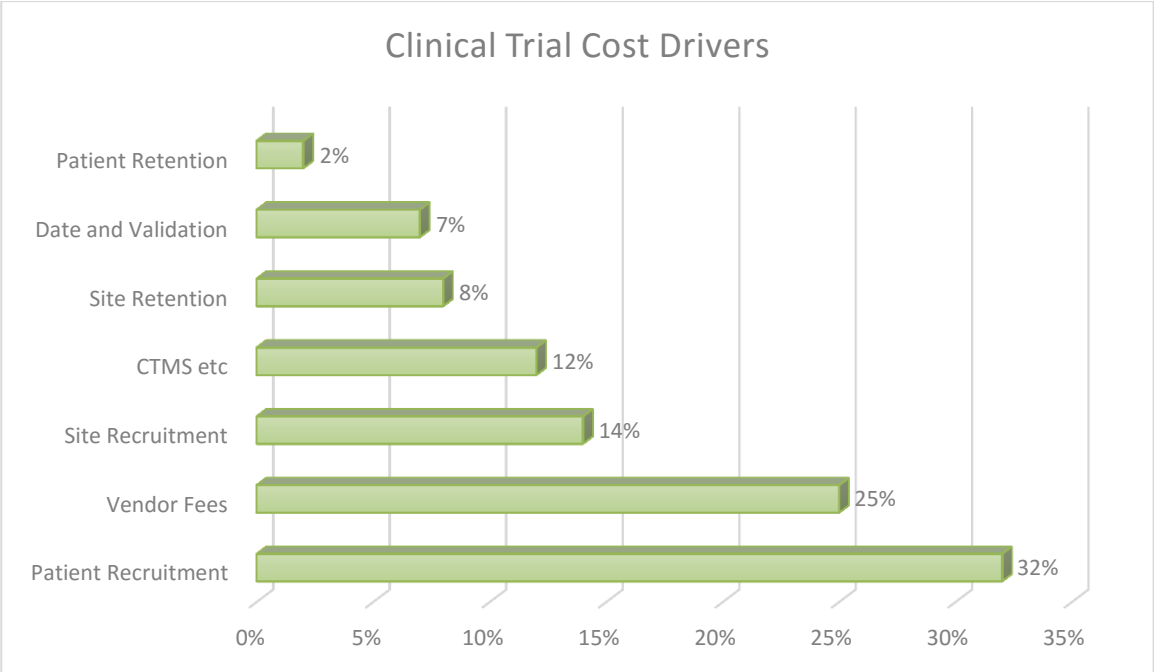

Fig. 3. Clinical Trial Cost Drivers. Ref: Trialfactas.com (Published on November 25, 2010)

Along with a rapidly growing number of international research centers, more investigators and more sites are involved in the process. Relationships between investigators and patients are changing often and this can further complicate the process planning.

In a survey conducted in the USA, 32% of the drug development budget was related to patient activities such as participation, retention, incentives, etc. An extension in an international trial due to insufficient patient numbers resulted in a $ 1.3 million additional cost per day.

Identifying the Issue

Patient processes are the largest item in the research budget. We can review the process in two main stages: patient recruitment and retention.

Research patient recruitment contains the following processes:

1. Patient screening
2. Achieving patient consent
3. First visit and randomization

For patient screening, many methods are used, such as associations, social media, written and visual marketing, etc. Still, the most common method is working directly with healthcare centers and their comprehensive patient archive. For example, in Turkey, medical faculties are chosen for their familiarity to research culture and broad portfolio of patients, particularly in rare diseases.

A health center's archive brings great opportunities along with big challenges. Maintaining quality in an ongoing archive is an important issue. However, archival quality is increasing, in part, due to malpractice concerns. Since the widespread use of hospital information systems (HIS), there have

been significant improvements.

In addition, archive screening requires an effort and financial cost. The process is labor-intensive and considered to be unappealing. Junior residents, students, medical secretaries and site coordinators generally execute this screening, with unsatisfactory performance. The reasons vary according to the scanner: The main reasons are a lack of medical knowledge and an insufficient knowledge of the research protocol.

Most of the staff execute the screening based on one or two criteria and thus may skip eligible patients for various reasons. Unfortunately, with this manual screening method effectiveness and sensitivity cannot be evaluated with any precision.

Furthermore, with manual screening it is difficult to reach current patient records. Manual screening will take days, perhaps weeks, to perform. A lack of controls and an inability to cover the whole institution's archive are added major concerns.

Solution Suggestion: IT Support

Nearly 30% of the time dedicated to clinical trials is spent on patient recruitment and enrollment, while 37% of all sites in a given trial fail to meet their enrollment targets and more than 10% never enroll a single patient. As electronic technologies have redefined many processes in various industries, it is clear that such enhancements are also needed in clinical research.

Electronic Health Records (EHRs) may leverage the speed and quality of the patient recruitment process. The pharmaceutical industry and healthcare organizations are looking for an interoperable platform that utilizes real-time data from EHRs for clinical research, in compliance with relevant legal, ethical, regulatory, privacy protection requirements and policies.

There is no question that recruiting patients for global clinical trials through traditional means alone is challenging, time-consuming and expensive. However, integrating an intelligent system to the available HIS would help to scan the entire online data in seconds and, in turn, boost success rates. This is certainly incomparable to the manual process that requires days of extensive efforts. With such systems, data could be analyzed fast and efforts to reach eligible patients would be reduced to the minimum.

PRS

Patient Recruitment System is one of the best innovative examples in clinical research. It is an integrated electronic system for recruitment in clinical trials. With the help of an Ontology Management Service (OMS), PRS utilizes patient EHR and enriches the data by harmonization, normalization and mapping to international classification systems and terminology. An indexing mechanism gives PRS the power to search for eligible patients among the millions of patient data in seconds, without affecting the performance of ongoing HIS operations.

PRS offers significant opportunities for the advancement of clinical research and enable clinical trials to be conducted more efficiently and cost effectively, by following the international data

privacy and confidentiality principles.

This intelligent system is installed at each site and controlled by the site IT. As a privacy measure, the system is only accessible by users within the premises of the institution. PRS applies a pseudonymisation technique to patient data in order to fulfill research requests while safeguarding the privacy of individuals.

PRS has three main features:

1. Protocol authoring
2. Feasibility
3. Real-time recruitment

With the protocol authoring feature, PRS enables sponsors and investigators to validate and optimize their protocols based on actual, real-time patient data on a hospital, regional, national or international level.

In the feasibility feature, for a defined study protocol, the EHR databases in a given site are screened to assess how many suitable patients can be expected in a certain time period.

With the real-time recruitment feature, PRS continues the screening process regularly. Located eligible patients will be reported immediately to the relevant investigator and study team. PRS identifies 8 to 30 times more patients compared to manual screening. It can run hundreds of clinical protocols in parallel and notify the study teams for eligible patients within the scheduled periods. This shows the efficiency of technology-supported screening.

Ultimately, increasing the number of PRS installed institutions will support Sponsors' rational site selection. The eligible patient volume of the center will be evaluated with a realistic feasibility. This way, the cost for site selection will be reduced radically and become a more manageable part of the research budget.

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