CLINICAL TRIALS APPLICATION MANAGEMENT

DISSERTATION REPORT

A Dissertation report submitted in partial fulfilment of the requirements for the award of

Post-Graduate Diploma in Health and Hospital Management

By

Dr Amit Kumar Srivastava
Roll No. PG/11/009

International Institute of Health Management Research, New Delhi-110075

Dell International Services India Pvt Ltd
Plot No. 123, EPIP Phase II,
Whitefield Industrial Area,
Bengaluru – 560066, Karnataka, India.
Tel : + 91 80 2841 3000
www.dell.com/services

CERTIFICATE OF DISSERTATION COMPLETION

To Whomsoever It May Concern

April 14, 2013

This is to certify that **Dr. Amit Kumar Srivastava** has successfully completed his 3 months internship in our organization from January 14th 2013 to April 14th 2013. During this tenure, the intern has worked on **"Clinical Trials Application Management"** under the guidance of me and my team at **DELL International Services, Bangalore.**

We wish him good luck for his future assignments.

Regards,

Adarsh Naik

Adarsh Naik

Talent Acquisition Manager II

Regd. Off.: Plot No. 123, EPIP Phase II, Whitefield Industrial Area, Bengaluru - 560 066, Karnataka, India

Dell International Services India Pvt Ltd
Plot No. 123, EPIP Phase II,
Whitefield Industrial Area,
Bengaluru – 560066, Karnataka, India.
Tel : + 91 80 2841 3000
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CERTIFICATE OF APPROVAL

The following dissertation titled **"Clinical Trials Application Management"** is hereby approved as a certified study in management carried out and presented in a manner satisfactory to warrant its acceptance as a prerequisite for the award of **Post-Graduate Diploma in Health and Hospital Management with Specialization in Healthcare IT** for which it has been submitted. It is assumed that by this approval, the undersigned do not necessarily endorse or approve any statement made, opinion expressed, or conclusion drawn therein but approve the dissertation only for the purpose it is submitted.

Dissertation Examination Committee for evaluation of dissertation

Name	Signature
Vivek Vig	
AVANISH KR. SINGH	
T. Bhattacharya	

Dell International Services India Pvt Ltd
Plot No. 123, EPIP Phase II,
Whitefield Industrial Area,
Bengaluru – 560066, Karnataka, India.
Tel : + 91 80 2841 3000
www.dell.com/services

Certificate from Dissertation Advisory Committee

This is to certify that **Dr. Amit Kumar Srivastava**, a graduate student of the **Post-Graduate Diploma in Health and Hospital Management** has worked under our guidance and supervision. He is submitting this dissertation titled **"Clinical Trials Application Management"** in partial fulfillment of the requirements for the award of the **Post-Graduate Diploma in Health and Hospital Management.**

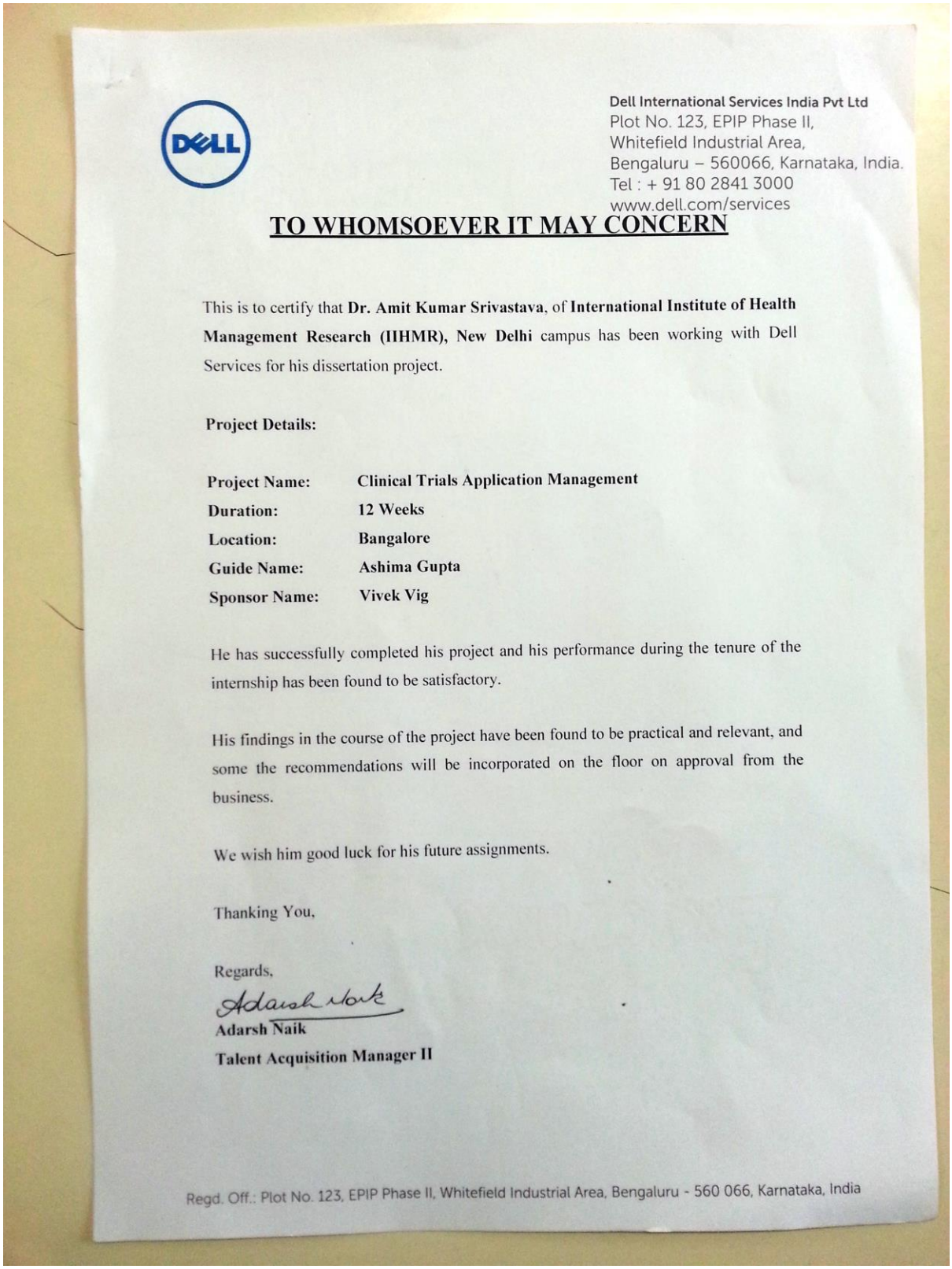
This dissertation has the requisite standard and to the best of our knowledge no part of it has been reproduced from any other dissertation, monograph, report or book.

Faculty Mentor:
Dr. T Muthu Kumar
Professor
IIHMR
Date 4/5/2013.

Indrajit Chatterjee
Professor, Healthcare IT
International Institute of Health Management Research
Plot No. - 3, HAF Pocket, Phase-II,
Sector-18A, Dwarka, New Delhi-110075

Organizational Advisor:
Ashima Gupta
Business Systems Advisor
Dell Services – Noida
Date

Regd. Off.: Plot No. 123, EPIP Phase II, Whitefield Industrial Area, Bengaluru - 560 066, Karnataka, India



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Bengaluru – 560066, Karnataka, India.
Tel : + 91 80 2841 3000
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TO WHOMSOEVER IT MAY CONCERN

This is to certify that **Dr. Amit Kumar Srivastava**, of **International Institute of Health Management Research (IIHMR), New Delhi** campus has been working with Dell Services for his dissertation project.

Project Details:

Project Name:	**Clinical Trials Application Management**
Duration:	**12 Weeks**
Location:	**Bangalore**
Guide Name:	**Ashima Gupta**
Sponsor Name:	**Vivek Vig**

He has successfully completed his project and his performance during the tenure of the internship has been found to be satisfactory.

His findings in the course of the project have been found to be practical and relevant, and some the recommendations will be incorporated on the floor on approval from the business.

We wish him good luck for his future assignments.

Thanking You,

Regards,

Adarsh Naik

Adarsh Naik
Talent Acquisition Manager II

Acknowledgement

I hereby take this opportunity to thank, Mrs Ashima Gupta, Senior Business Advisor, Dell Services for the valuable guidance and advice. She inspired me greatly to work on this project. Her willingness to motivate contributed tremendously.

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Finally, an honourable mention goes to my family and friends for their understanding and support on me in completing this project.

Thank You

Dr Amit Kumar Srivastava

PGDHHM,

IIHMR, New Delhi.

ACRONYMS / ABBREVIATIONS / KEYWORDS

- CTMS — Clinical Trial Management Systems
- CDMS — Clinical Data Management Systems
- APAC — Asia-Pacific Region
- CROs — Contract Research Organisation
- CRAs — Clinical Research Associates
- CT — Clinical Trials
- FDA — US Food Drug Administration
- NCE — New Chemical Entity
- NDA — New Drug Application
- PK/PD — Pharmacokinetics, Pharmacodynamics
- EC — Ethics Committee
- IRB — Institutional Review Board
- SaaS — Software as a service
- EDC — Electronic data capture
- CDM — Clinical data management
- CRF — Case report forms
- IVRS — Interactive Voice Response System
- CRF — Code of Federal Regulations
- SCDM — Society for Clinical Data Management
- GCDMP — Good Clinical Data Management Practices
- CDISC — Clinical Data Interchange Standards Consortium
- SDTMIG — Study Data Tabulation Model Implementation Guide for Human Clinical Trials
- CDASH — Clinical Data Acquisition Standards Harmonization
- eCRF — Electronic case report forms
- eCTD — Electronic Common Technical Document
- ePRO — Electronic patient reported outcomes
- RFID — Radio Frequency Identification technologies
- SPL — Structured Product Labelling
- HL7 — Health Level Seven
- XML — Extensible mark-up language
- eCTD — Electronic Common Technical Document
- ISS — Integrated Safety Summary
- ISE — Integrated Summary of Effectiveness

Note: Listed in order of appearance

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PART I

INTERNSHIP REPORT

1.1 ORGANISATION PROFILE

DELL SERVICES

Dell Inc. (Dell) is a global information technology company that offers its customers a range of solutions and services delivered directly by Dell and through other distribution channels. Dell is a holding company that conducts its business worldwide through its subsidiaries.(1) Dell Inc. was founded in 1984 and is headquartered in Round Rock, Texas. Dell traces its origins to 1984; when Michael Dell created PCs Limited while a student at the University of Texas at Austin. The dorm-room headquartered company sold IBM PC-compatible computers (2) built from stock components. Dell dropped out of school in order to focus full-time on his fledgling business, after getting about $300,000 in expansion-capital from his family.

In 1985, the company produced the first computer of its own design, the "Turbo PC", which sold for US$795. PCs Limited advertised its systems in national computer magazines for sale directly to consumers and custom assembled each ordered unit according to a selection of options. The company grossed more than $73 million in its first year of operation.

The company changed its name to "Dell Computer Corporation" in 1988 and began expanding globally. In June 1988, Dell's market capitalization grew by $30 million to $80 million from its June 22 initial public offering of 3.5 million shares at $8.50 a share. In 1992, Fortune magazine included Dell Computer Corporation in its list of the world's 500 largest companies, making Michael Dell the youngest CEO of a Fortune 500 company ever.(3)

Dell has grown by both increasing its customer base and through acquisitions since its inception; notable mergers and acquisitions including Alienware(2006) and Perot Systems (2009). As of 2009, the company sold personal computers, servers, data storage devices, network switches, software, and computer peripherals. Dell also sells HDTVs, cameras, printers, MP3 players and other electronics built by other manufacturers. The company is well known for its innovations in supply chain management and electronic commerce. (3)

Perot Systems was an information technology services provider founded in 1988 by a group of investors led by Ross Perot and based in Plano, Texas, United States. A Fortune 1000

corporation with offices in more than 25 countries, Perot Systems employed more than 23,000 people and had an annual revenue of $2.8 billion before its acquisition in 2009 by Dell, Inc. for $3.9 Billion.(4)

Perot Systems provided information technology services in the industries of health care, government, manufacturing, banking, insurance and others. Perot Systems was especially strong in health care industries with services such as digitizing and automating medical records.(4)

The integration of Perot Systems has strengthened Dell Services, expanded its portfolio of capabilities, and established a strong foundation for future growth. The combined Dell Services business unit represents almost $8 billion in annual revenue. With more than 43,000 team members working in 90 countries, Dell Services operates 60 technology support centers around the world, 36 customer data centers and provides technical support for 14 million client systems and 10,000 Software-as-a-Service (SaaS) customers. Over the past year, the Services team met or exceeded all of its integration milestones, achieving more than $100 million in cost savings in fiscal year 2011 and capturing revenue synergies of more than $150 million, both surpassing original estimates.(5)

At February 3, 2012, it held a worldwide portfolio of 3,449 patents and had an additional 1,660 patent applications pending. The Company also holds licenses to use numerous third-party patents. The Company designs, develops, manufactures, markets, sells, and supports a range of products, solutions, and services. It also provides various customer financial services to its Commercial and Consumer customers. During fiscal year ended February 3, 2012 (fiscal 2012), Dell acquired Compellent Technologies, Inc. (Compellent), SecureWorks Inc. (SecureWorks), Dell Financial Services Canada Limited and Force10 Networks, Inc. (Force10). In February 2012, the Company acquired AppAssure. In April 2012, the Company acquired Clerity Solutions.(6)

1.2 AREA OF ENGAGEMENT

The area of engagement in the organisation was in EMR support team of DELL. Initially I was engaged in training of Meditech and McKesson EMR for 2 weeks and then got training on

Cerner core application for next 3 weeks. I was assigned the task of studying and analysing clinical trials. Based on the analysis, I was assigned to prepare a structure of Clinical trial application support and management. I was assigned to perform Cerner Charting validation based on the given script. Meanwhile I got an opportunity to work on Cerner tools as per the work assigned.

1.3 MANAGERIAL TASKS INVOLVED

Management is required for every small, big developing organisation who wants to be successful. Even the smallest tasks require a managerial skill to handle it otherwise all the pain may go in vain if not managed properly.

Some of the tasks that were performed are as follows:

Currently part of Cerner core team which provide functional support, file building, documentation and management of HIS. Also provide level 2 support in response to user problems and questions regarding system functionality, operations, input/output, reporting and general operational procedures. Many other tasks apart from the above mentioned tasks were also assigned from time to time.

1.4 REFLECTIVE LEARNINGS

As a Business Systems Analyst at DELL International Services, I have gained valuable knowledge in terms of application of managerial and analysis skills in real practical world. It helped me to develop the skills and knowledge which are must everyone who wants to carve in his career as successful professional.

PART II

DISSERTATION REPORT

ON

CLINICAL TRIAL APPLICATION MANAGEMENT

CHAPTER 1: PREFACE

Clinical trials are required globally to decrease illness load by assisting to develop reliable and efficient novel remedies and vaccines. The present solutions may be because non-communicable disorders like malignancy as well as diabetes or, for communicable diseases as they are required especially in the poorest countries of the globe. As an investigational tool, clinical trials are crucial for developing new outcomes by attaining the data demanded by regulators, either it is for product grant extensions, for existing remedies, for typical diseases or to deliver cutting edge brand-new therapies and vaccines into certified practice.

The World Health Organization defines clinical trials as ‘‘any investigational study that prospectively commissions human participants or groups of individuals to one or more health associated interventions to measure the result on health outcomes’’.

The way the biopharmaceutical manufacturers conducts clinical trials are experiencing a remarkable change. Coupled with this much needed growth are unique challenges particular to the increasing role that information technology (IT) will play to enable the new clinical development landscape.

Of the various challenges facing the biopharmaceutical industry this moment, the important demand for higher operational efficiency in clinical drug development is paramount. With flat and even decreasing productivity, increasing research and development (R&D) costs, more complex preapproval trials and extensive post-approval research driven by the shift toward biological agents, and increasing regulatory demands, it is necessary that clinical trials are conducted more effectively and efficiently. While progress has been made in addressing these challenges, organizations are more shifting to clinical trial management systems (CTMS) & clinical data management systems (CDMS) to improve trial efficiencies, reduce trial costs, and increase the efficiency of trial participants.

There are numerous advantages to be recognized from having a clinical trial management system (CTMS) & clinical data management systems (CDMS). It serves as a primary

repository for all best practices and company-specific information, as well as providing a way to manage and streamline clinical operations.

As clinical trials develop into larger and more complex, there is growing pressure on a company's ability to manage them efficiently. This has led to the need for clinical development firms to implement new technologies such as clinical trial management systems (CTMS) & clinical data management systems (CDMS) to improve workflow efficiency and improve clinical data management operations. Furthermore, firms can maximize the potential of systems such as these by using them in innovative ways to shorten the time and costs required to complete a drug through development.

An effective CTMS can overcome communication overheads, support protocol feasibility, expedite the management of investigative sites, cut down on administration, and save money in the process—something of utmost importance in the current economic climate.

CHAPTER 2: PROBLEM STATEMENT

This dissertation is based on Clinical trials and its management with the help of IT tools. CTMS & CDMS are the tools which enable data analysis and its management in more meaningful manner.

2.1 RATIONAL OF THE STUDY

This is the first attempt to understand the entire clinical trials process flow from laboratory to market (Drug Discovery Process) and understand the challenges and opportunity of IT in clinical trials and Understand global perspective of Clinical trials, Drug development Phases, development cost & Time taken to complete the research. Driving Forces Accelerating Information Technology towards CTMS / CTMS. CTMS & CDMS key features, regulations, tools, market & overall benefits of its adoption.

CHAPTER 3: REVIEW OF LITERATURE

UNDERSTANDING CLINICAL TRIALS-GLOBAL PRESPECTIVE

The data for clinical trial is usually gathered from discrete populations to uphold a license application because geographically differing trial sites are required to guarantee that the manufactured product is harmless as well as works in the same form for different ethnic groups. This requirement holds valid whether it is for a pharmaceutical company which is working on the next blockbuster drug or for a not-for-profit cooperation (which typically have a pharmaceutical ally associated in a non-for-profit capacity) which is developing an innovative remedy or vaccine for a neglected illness. In this place, scientific as well as regulatory factors unite to encourage the globalization of clinical trials, so that it can be accepted worldwide. Moreover, Clinical trials are conducted across diverse countries due to financial reasons. (7)

Clinical trials are expensive and are taking a longer time as compared to the past, thus further compounding the cost, moreover this is the state for all kinds of trial, in case commercial or academic. There are numerous reasons for inflation in duration and cost of clinical trials but it is a broadly held view that clinical regulations, or more specifically, the interpretation and implementation of these regulations, is a significant factor. (7)

It is of utmost importance that the clinical trials be well-regulated to ensure high ethical standards and that the trial conduct and process produce valid and accurate data, but, there is a request for making trial regulation less complex and more easily adaptable to risk, as well as for having guidelines that are globally relevant and adaptable for all sorts of trial. (7)

Such guidelines would be as quickly implemented to pragmatic trials of existing therapies or disease management questions as they would be for trials of novel drugs as well as vaccines.

There are numerous justifiable bases for running clinical trials across various nations or indeed continents, or even just in sites that are not in the sponsor’s location. A few nations are able to recruit participants quickly than others for discrete and credible reasons. (7)

The trial could be for an unusual health incident, such as dengue fever or traumatic cerebral haemorrhage, and for these trials it is necessary to recruit many centres in diverse locations, each site can then recruit just a few patients to avoid an addition in the span of the trial and raise in wait for novel interventions. (7)

It is also correct that some countries of the globe are much more costly than others to conduct trials. For instance, a clinical trial in India can require one-tenth of the expense that it would cost in the US. Since clinical trials costs are mainly driven by labour, much of these savings are from lower wages to doctors, nurses, and trial supervisors. (7)

The period and cost of developing new drugs or vaccine affects the cost and revenue on investment of the final outcome and, so the logic of decreasing trial expenses by going global is obvious and reasonable.

Besides cost reduction following points explain the benefits of clinical trials go global:

- Clinical experiments are carried across the globe for absolutely good reasons. This holds positive because populations in developing countries are under-represented in research.

- Due to the value of increased capacity development and investment, research sites in developing countries benefit from working with externally sponsored clinical trials.

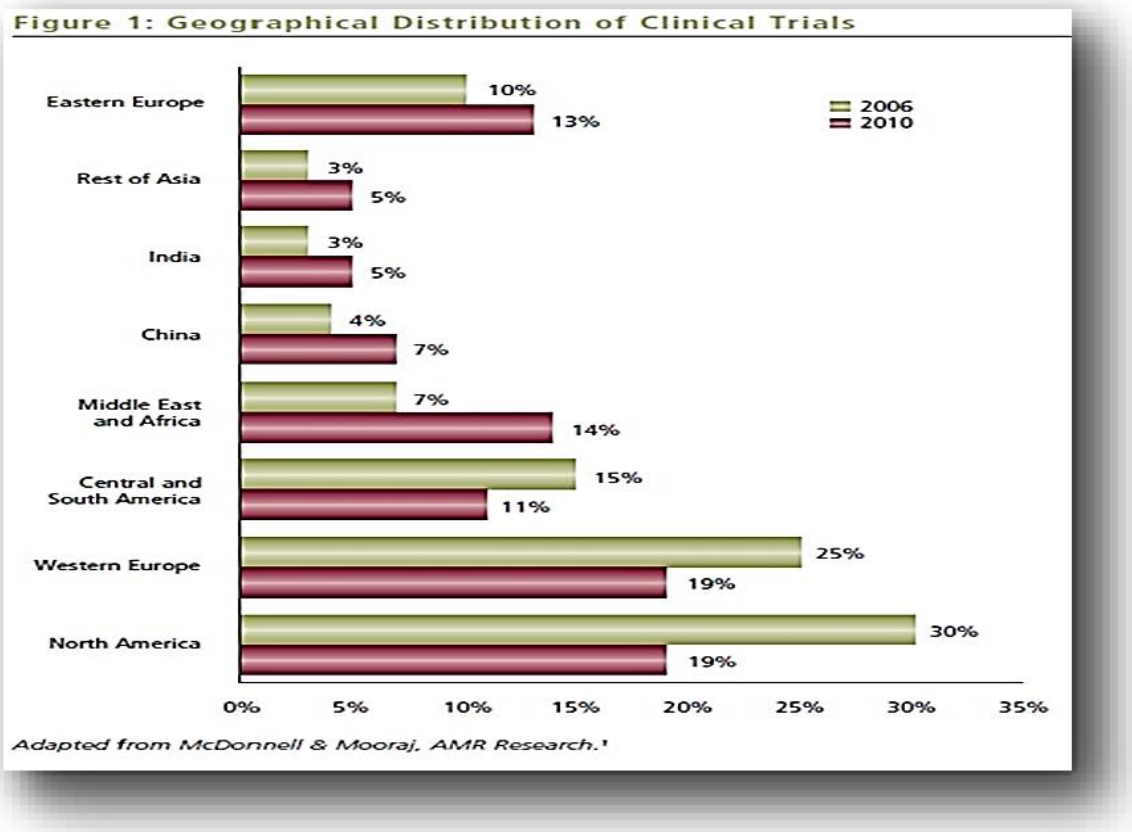
- Locally led research is becoming harder to undertake due to complex trial regulations. So, there should be a balance between local as well as externally led trials.

- There is a demand for expanded trials that can relate different approaches to manage illness and health issues. This is particularly valid in low-income settings where simple interventions could produce meaningful improvements to health outcomes, provided there is evidence to support implementation.

- Clinical trial operations should be specific to the risk and complexity of each trial and should not be governed by one-size-fits-all requirement of sponsors as well as their

contracted organisations. Overly burdening clinical trials with too-rigorous preliminary condition are pushing up charges and putting off researchers to begin research. (7)

The global clinical trial, though not new to either sponsors or clinical research organizations (CROs), is becoming more common. Clinical trials are expanding in size and complexity and more global trials are being conducted across different geographical territories. The predicted trend is that there will be a substantial transformation from North America/Western Europe to the Asia-Pacific region (APAC). Between 2008 and 2010 the rate of trials managed in North America/Western Europe is expected to fall from 55 to 38% (see Figure 1).



Clinical trials managed in Asia-Pacific region (APAC) offers potential cost savings as well as vast patient populations, especially treatment-naive subjects.

This transformation in between regions will also have certain implications. Sponsors and CROs will have to support all operational aspects of global trials: language, logistic, access control, regional requirements, local regulatory requirements and region-specific business processes.

To manage global trials more efficiently, many companies are turning to commercial CTMS (clinical trial management system). These CTMS are typically implemented as enterprise applications. (7)

The fundamental value proposition of CTMS is the provision of a centralized trial repository, which enforces standard trial management processes across the enterprise and provides geographically diverse end-users with real-time data visibility into study progress, but role based access should be provided to ensure security and privacy of data and information. (7)

Organizations should balance the access to available information with tight control over data access, allowing only those with proper authorization to get access to the appropriate files. Fortunately, technology solutions exist that provide the access control necessary for the clinical trial industry, as well as tools that significantly reduce the administrative overhead. (7)

The globalization of clinical trials needs to be truly worldwide rather than just a process of more trials conducted in different locations. This will require global unified system with built-in functionality that supports specific regional needs. The current mind-set, however, is still more or less focused toward the traditional North America/Western Europe requirements and supporting prevailing business needs. (7)

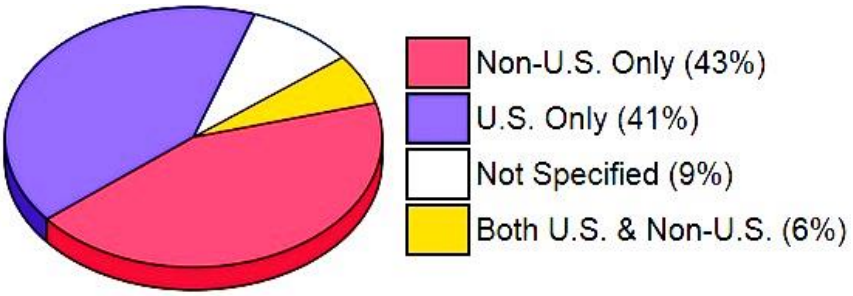
For a truly global system, this view needs to be changed to ensure that individuals and departments have a clear understanding of where they fit into the business process. Regional units need to understand that their work affects others in the process, so that accordingly, effective collaborations can take place. It is also important to assess the impact that local infrastructure and culture may have on conducting clinical trials in developing countries. (7)

Understanding the local environment and requirements often drives innovation that brings substantial impact. Innovative solutions that are very site-focused, very pragmatic, and very specific to the local infrastructure may overcome barriers. For example, patient follow-up is a significant issue in China. A large Chinese CRO has proposed utilizing mobile technology, in the form of cell phones, as a component of its site management system. The proposed system would allow stakeholders to send the alerts or messages via SMS, or push reminders to patients regarding visits. This form of collaborative tool, along with better data visibility, will help clinical research associates (CRAs) better manage their sites and increase study compliance.(7)

Another recent trend is the growing demand from regulatory agencies in the US, Europe, and Japan for large-scale post-marketing studies as a condition for approval. Indeed, according to Tufts, between 1998 and 2008, 75% of new drugs approved in the US and the EU, and 50% of those approved in Japan, had post-marketing study commitments attached to the approvals. Post-marketing studies are typically much larger in scale, with hundreds or even thousands of sites and many more patients. Managing large-scale trials carry unique challenges. (7)

While pre-marketing studies focus on data quality for each individual patient, post-marketing studies place greater emphasis on sampling and automation. CTMS that have built-in workflows and can be easily set up and modified is well suited for post-marketing studies. Therefore, integration with safety surveillance systems that allow both pre-marketing and post-marketing safety data to be viewed holistically and longitudinally will become increasingly necessary. (7)

Industry-sponsored clinical research has traditionally been carried out in relatively wealthy locations in North America, Western Europe and Oceania. However, in recent years, a shift in clinical trials sponsored by the biopharma industry to so-called emerging regions, especially in Eastern European, Latin American and Asian countries, has been noted.



Location	Number of Registered Studies and Percentage of Total
Non-U.S. Only	61,819 (43%)
U.S. Only	58,925 (41%)
Not Specified*	13,241 (9%)
Both U.S. & Non-U.S.	9,103 (6%)
Total	143,088

* Not Specified: The location of the study was not provided by the Sponsor.

(Data as of April 05, 2013)

Figure 2: Locations of Registered Studies

Reference: ClinicalTrials.gov currently lists 143,088 studies with locations in all 50 states and in 182 countries.

Reasons cited for this shift include the ability to reduce operational costs while recruiting a large number of patients in a timely manner; the establishment of contract research organizations focused on global clinical trials; the rapid pace of growth of market size, research capacity and regulatory authority in emerging regions; and the harmonization of guidelines for clinical practice and research. (7)

It seems that these factors will continue to be prominent drivers of the globalization process, resulting in the solidification of trends and increased geographic dispersion of drug development operations.

The globalization of clinical trials can bring both health benefits and hazards to research subjects and the general population. Potential benefits include diffusion of medical knowledge and effective medical practice, and greater patient access to high quality medical care. Concerns include the possibly inadequate regulatory oversight of research activities in emerging regions and the difficulty in drawing valid scientific conclusions with pooled data from ethnically and culturally diverse populations. Additional areas of concern include ethical issues involving integrity of the informed consent process and suitability of the clinical research focus, and economic impacts from the shift of geographic allocation of CTs for the associated countries and companies. (7)

CHAPTER 4: OBJECTIVES

4.1 GENERAL OBJECTIVE

To study the Clinical Trials Application Management

4.2 SPECIFIC OBJECTIVE

- To understand clinical trials global perspective
- To study the drug development process flow, cost, time and its development phases.
- To analyse the driving forces accelerating information technology
- To study CTMS/ CDMS and its key features
- To understand the regulations applicable in clinical trials
- To study the role of it in improving clinical trials
- To understanding challenges & opportunities in implementing it
- To study the tools, market and its overall benefits of adoption

CHAPTER 5: METHODOLOGY

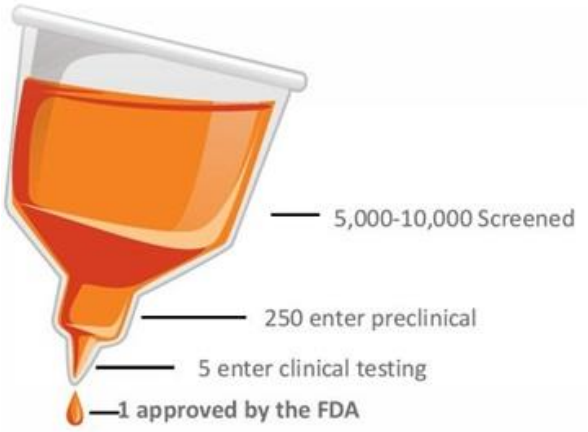
5.1 Study Design: Secondary/ Descriptive

5.2 Description

Week	Activity	Output
1	Project structure	Report generated
2	Understanding global clinical trials	Report generated
3	Drug development cost/ time	Report generated
4	Drug development process flow	Report generated
5	Clinical Development phases	Report generated
6	Driving forces accelerating IT	Report generated
7	CTMS/CDMS	Report generated
8	Improving CT by Implementing IT	Report generated
9	Understanding Challenges & Opportunities	Report generated
10	CTMS/CDMS Tools, Market	Report generated
11	Overall Benefits of adoption	Report generated
12	Market players, product description, Conclusion, recommendation	Report generated

DRUG DEVELOPMENT

Drug development is a blanket term used to define the process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the step of obtaining regulatory approval to market the drug. (8)



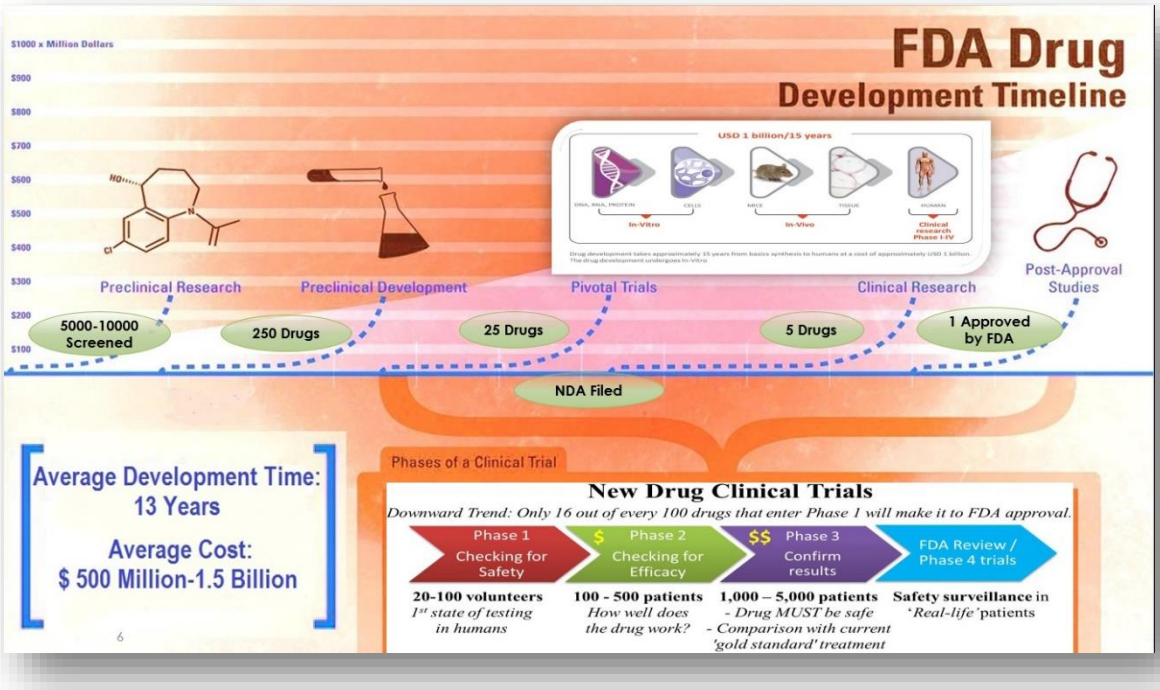
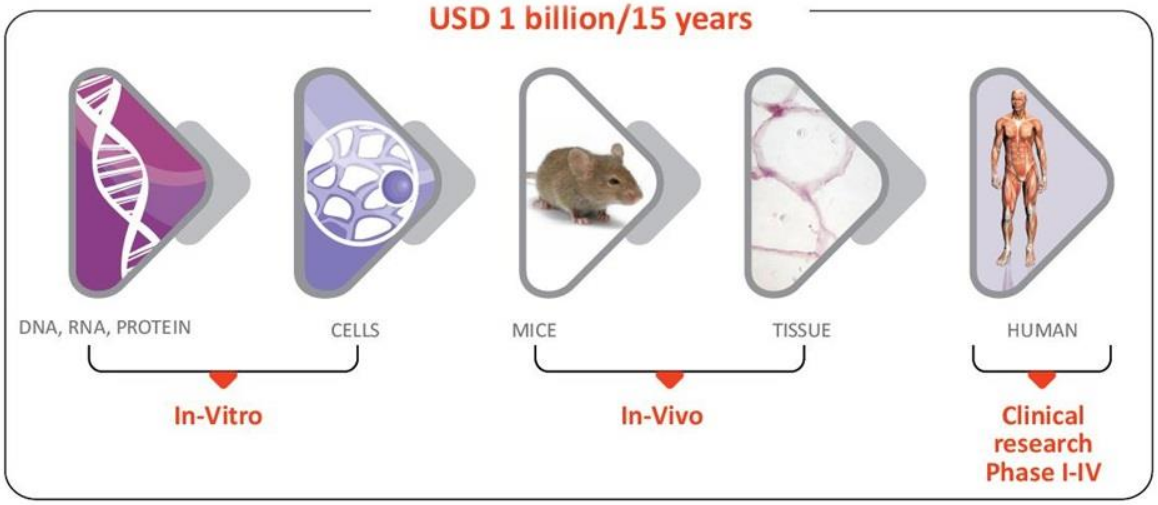


Figure 3: Drug Discovery Process

DRUG DEVELOPMENT COST

The full cost of bringing a new drug (i.e. a drug that is a new chemical entity) to market - from discovery through clinical trials to approval - is complex and controversial. One element of the complexity is that the much-publicized final numbers often do not include just the simple out-of-pocket expenses, but also include "capital costs", which are included to take into account the long time period (often at least ten years) during which the out-of-pocket costs are expended; additionally it is often not stated whether a given figure includes the capitalized cost or comprises only out-of-pocket expenses. Another element of complexity is that all estimates are based on confidential information owned by drug companies, released by them voluntarily. There is currently no way to validate these numbers. The numbers are controversial, as drug companies use them to justify the prices of their drugs and various advocates for lower drug prices have challenged them. The controversy is not only between "high" and "low" -- the numbers also vary greatly at the high end. (8)



Drug development takes approximately 15 years from basics synthesis to humans at a cost of approximately USD 1 billion. The drug development undergoes In-Vitro

Figure 4: Drug Discovery Timeline

A study published by Steve Paul *et al.* in 2010 in Nature Reviews: Drug Discovery compares many of the studies, provides both capitalized and out-of-pocket costs for each, and lays out

the assumptions each makes. The authors offer their own estimate of the capitalized cost as being ~$1.8B, with out-of-pocket costs of ~$870M.

Studies published by diMasi *et al.* in 2003, report an average pre-tax, capitalized cost of approximately $800 million to bring one of the drugs from the study to market. Also, this $800 million dollar figure includes opportunity costs of $400 million. A study published in 2006 estimates that costs vary from around $500 million to $2 billion depending on the therapy or the developing firm. A study published in 2010 in the journal Health Economics, including an author from the US Federal Trade Commission, was critical of the methods used by diMasi *et al.* but came up with a higher estimate of ~$1.2 billion.(8)

DRUG DEVELOPMENT TIME /LENGTH

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.(9)

For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials. But the major holdup in making new cancer drugs available is the time it takes to complete clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public. Drugs for other diseases have similar timelines.(10)

Some reasons a clinical trial might last several years:

- For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.
- For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.

- Only certain people who have the target disease condition are eligible to take part in each clinical trial.(10)

DRUG DEVELOPMENT PROCESS FLOW

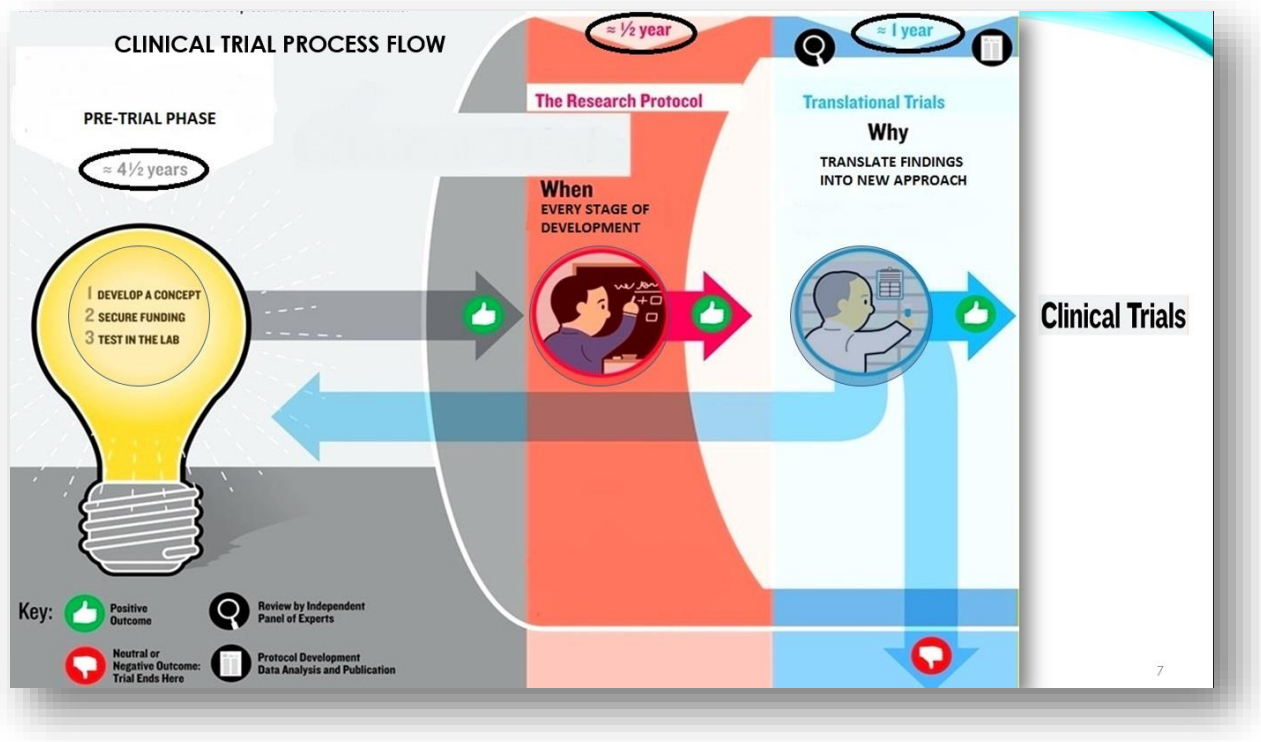


Figure 5-A: Drug Development Process Flow

CLINICAL DEVELOPMENT (Clinical Trials)

The process of drug development does not stop once an NCE begins human clinical trials. In addition to the tests required to move a novel drug into the clinic for the first time it is also important to ensure that long-term or chronic toxicities are determined, as well as effects on systems not previously monitored (fertility, reproduction, immune system, etc.). The compound will also be tested for its capability to cause cancer (carcinogenicity testing).(8)

If a compound emerges from these tests with an acceptable toxicity and safety profile, and it can further be demonstrated to have the desired effect in clinical trials, then it can be submitted for marketing approval in the various countries where it will be sold. In the US, this process is

called a New Drug Application or NDA. Most NCEs, however, fail during drug development, either because they have some unacceptable toxicity, or because they simply do not work in clinical trials.(8)

Clinical trials are arrays of experiments in medical exploration and drug development that produce safety and efficacy records for health interventions. They are conducted only after satisfactory information has been gathered on the quality of the nonclinical safety, and health authority/ethics committee approval is granted in the country where approval of the drug or device is sought. Previously, many emerging countries did not require local trials for product approvals. Now, though emerging countries still accept data from U.S./Europe, they also require some local trials.(10)

Some examples of what a clinical trial may be designed to do:

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient (11)
- Assess the safety and effectiveness of a different dose of a medication than is commonly used (e.g., 10-mg dose instead of 5-mg dose) (10)
- Assess the safety and effectiveness of an already marketed medication or device for a new indication, i.e. a disease for which the drug is not specifically approved (10)
- Assess whether the new medication or device is more effective for the patient's condition than the already used, standard medication or device ("the gold standard" or "standard therapy") (10)
- Compare the effectiveness in patients with a specific disease of two or more already approved or common interventions for that disease (e.g., device A vs. device B, therapy A vs. therapy B) (10)

The most commonly performed clinical trials evaluate new drugs, medical devices (like a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before the national regulatory authority approves marketing of the drug or device, or a new dose of the drug, for use on patients. (10)

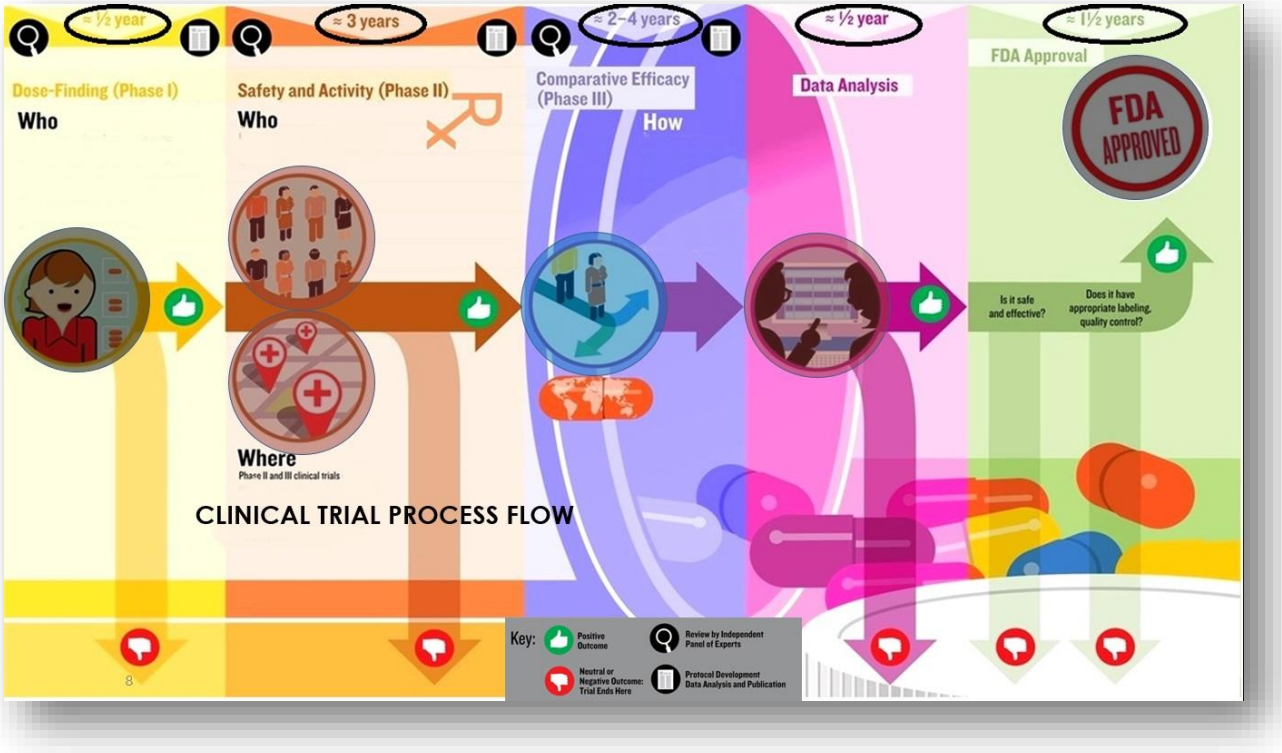


Figure 5-B: DRUG DEVELOPMENT PHASES

CLINICAL DEVELOPMENT PHASES

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases 1, 2, 3 and 4, it will usually be approved by the national regulatory authority for use in the general population.(10)

- Phase 1: Screening for safety
- Phase 2: Establishing the testing protocol
- Phase 3: Final testing
- Phase 4: Post approval studies (10)

Each phase has a different purpose and helps scientists answer a different question:

 Phase I Clinical Trials: Phase I clinical trials of approximately 20 subjects are designed to establish the safety and tolerability of the medicinal product and to define an optimum dose and schedule for Phase II studies and include trials on (12)

a) Estimation of Initial Safety and Tolerability

Phase I studies designed to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions.(12)

b) Pharmacokinetics

Pharmacokinetics is the characterisation of a drug's absorption, distribution, metabolism and excretion, which continues throughout the development plan. Preliminary characterisation is an important goal of Phase I. Pharmacokinetics may be assessed via separate studies or as a part of efficacy, safety and tolerance studies. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites and potential drug-drug interactions.(12)

c) Assessment of Pharmacodynamics

Depending on the drug and the endpoint studied, pharmacodynamics studies and studies relating drug blood levels to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients with the target disease. In patients, if there is an appropriate measure, pharmacodynamics data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies.(12)

d) Early Measurement of Drug Activity

Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage. (12)

 Phase II Clinical Trials: Phase II clinical trials of approximately 30 to 50 subjects are primarily aimed at determining the therapeutic efficacy of the medicinal product, but safety is also closely monitored as Phase II trials can provide additional information on cumulative drug dose toxicity. Initial therapeutic exploratory studies may use a variety of study designs, including concurrent controls and comparisons with baseline status. Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population and are closely monitored. An important goal for this phase is to determine the dose(s) and regimen for Phase III trials.(12)

 Phase III Clinical Trials: Phase III clinical trials involving usually 2000 to 5000 patients (for rare diseases, hundreds are acceptable) are intended to gather information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Randomised Phase III trials compare the medicinal product with the existing standard treatment for the disease in question. If the toxicity profile is acceptable and the efficacy compares favourably against existing standard treatments, then the medicinal product may be submitted to regulatory authorities for registration.(12)

 Phase IV Clinical Trials: Phase IV clinical trials are performed after drug approval and are related to the approved indication. They are trials that were not considered necessary for approval but are important for optimising the drug's use and collecting further toxicity data and contribute to post marketing safety surveillance by monitoring adverse reactions in a larger population.(12)

CHAPTER 6: RESULTS & FINDINGS

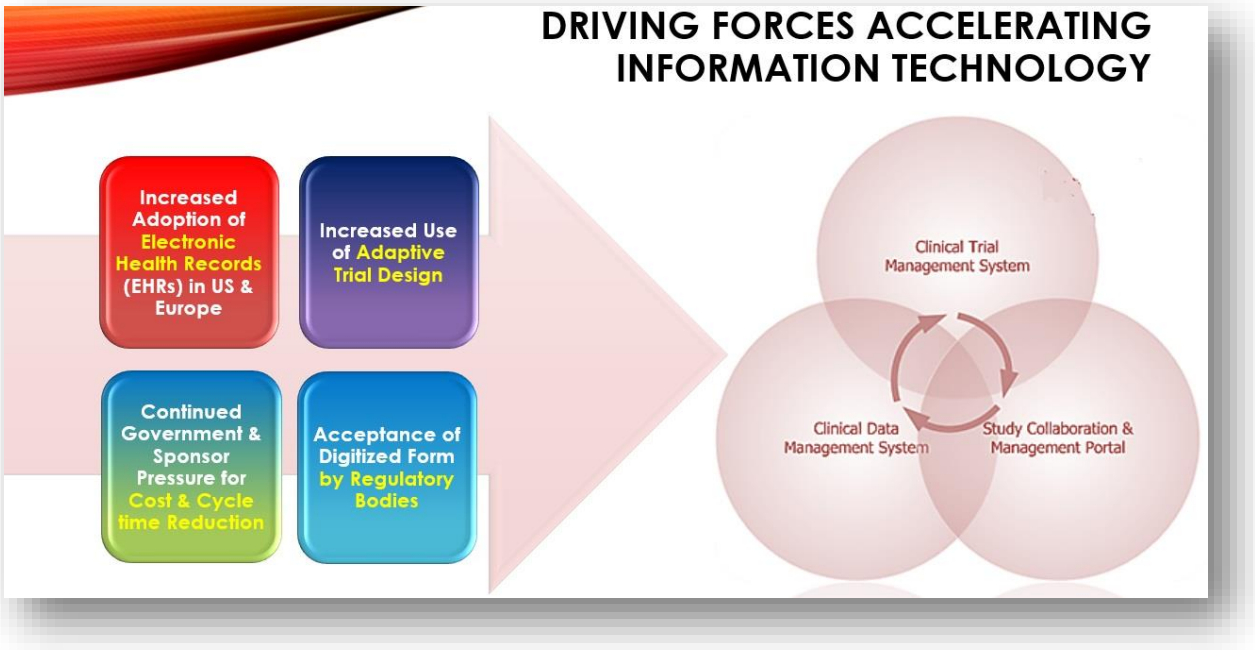


Figure 6: Driving forces accelerating IT

CLINICAL TRIAL MANAGEMENT SYSTEM (CTMS)

A Clinical Trial Management System, also known as CTMS, is a customizable software system used by the biotechnology and pharmaceutical industries and clinical research institutions to manage the large amounts of data involved with the operation of a clinical trial. It maintains and manages the planning, preparation, performance, and reporting of clinical trials, with emphasis on keeping up-to-date contact information for participants and tracking deadlines and milestones such as those for regulatory approval or the issue of progress reports. Often, a clinical trial management system provides data to a business intelligence system, which acts as a digital dashboard for trial managers.(13)

In the early phases of clinical trials, when the number of patients and tests are small, most managers use an in-house or home-grown program to handle their data. As the amount of data grows, though, organizations increasingly look to replace their systems with more stable,

feature-rich software provided by specialized vendors. Each manager has different requirements that a system must satisfy. Some popular requirements include: budgeting, patient management, compliance with government regulations, and compatibility with other data management systems.(13)

Each sponsor has different requirements that their CTMS must satisfy; it would be impossible to create a complete list of CTMS requirements. Despite differences, several requirements are pervasive, including: project management, budgeting and financials, patient management and recruitment, investigator management, EC/IRB approvals, compliance with U.S. Food and Drug Administration (FDA) regulations, and compatibility with other systems such as data management systems, electronic data capture, and adverse event reporting systems.(13)

In addition to pharmaceutical and biotechnology industries, CTMSs are also widely used at the sites where clinical research is conducted such as research hospitals, physician practices, academic medical centers and cancer centers.(13)

While pharmaceutical companies that sponsor clinical trials may provide a CTMS to the sites that participate on their trials, sites can also benefit from having their own CTMS to support their day-to-day operations in areas such as conducting study feasibility, streamlining the workflow of the trial coordinators and investigators, providing a centralized place to house all trial-related information, and making clinical data management more efficient by equipping staff, including biostatisticians and database administrators, with the time-saving tools necessary to optimize productivity.(13)

CTMS can take many forms. Some systems are cloud based and are delivered in a software as a service (SaaS) modality, while others require dedicated servers.(13)

Clinical trials are an expensive but essential part of a sponsor’s existence. Unless the articles are being tested in the most efficient (yet still safe and complete) way possible, costs of development can rapidly become excessive and needlessly increased. Because testing must include multiple phases and comply with many strict regulations (which also vary between countries), it is essential that companies efficiently organize and manage their trials. (14) With

the recent disclosures about problems with drugs on the market (such as Vioxx) and calls for investigation into others, sponsors now, more than ever, must be extremely vigilant in the eyes of both the regulatory bodies and the general public. That it is necessary for sponsors to implement controls that demonstrate their trial results cannot be questioned. If a sponsor contracts with a clinical research organization (CRO) to run a trial on the sponsor's behalf, the sponsor will most likely be looking for those controls from the CRO. The CRO's use of a CTMS to enforce adherence to the sponsor's rules will go a long way towards providing the needed reassurances.(15)

A CRO needs a tool that increases efficiency, productivity, capability, performance, and internal communication, as well as communication with the sponsor. A tool that helps decrease manpower, and administrative overhead also helps decrease associated costs. These benefits, in turn, can be passed on to a sponsor, giving the CRO a competitive edge. (16)

A CTMS is software specifically designed to track, structure, guide, conform, prompt, notify and report on trial progress and information. Consider it a "mission control" for clinical studies. Note that a CTMS is not designed to store or capture actual clinical trial data that is used to determine the efficacy of the item or items being studied. That is the job of Electronic Data Capture (EDC) software. A CTMS, in contrast, tracks the status of the people, events, data, finances and documentation involved in, and required for, the trial. It tracks planned activities and events to ensure that they occur, and notifies users about upcoming activities and events. A CTMS enables a CRO to be proactive rather than reactive where possible. It enables control of clinical trials in ways not possible when only spread-sheets or other manual processes are used.(17)

CLINICAL DATA MANAGEMENT SYSTEMS (CDMS)

A clinical data management system or CDMS is a tool used in clinical research to manage the data of a clinical trial. The clinical trial data gathered at the investigator site in the case report form are stored in the CDMS. To reduce the possibility of errors due to human entry, the systems employ various means to verify the data. Clinical data management can be a self-contained system or part of the functionality of a CTMS. A CTMS with clinical data

management functionality can help with the validation of clinical data as well as the help the site employ the data for other important activities like building patient registries and assist in patient recruitment efforts.(18)

Clinical Data Management (CDM) is a critical phase in clinical research, which leads to generation of high-quality, reliable, and statistically sound data from clinical trials. This helps to produce a drastic reduction in time from drug development to marketing. Team members of CDM are actively involved in all stages of clinical trial right from inception to completion. They should have adequate process knowledge that helps maintain the quality standards of CDM processes. Various procedures in CDM including Case Report Form (CRF) designing, CRF annotation, database designing, data-entry, data validation, discrepancy management, medical coding, data extraction, and database locking are assessed for quality at regular intervals during a trial. In the present scenario, there is an increased demand to improve the CDM standards to meet the regulatory requirements and stay ahead of the competition by means of faster commercialization of product. With the implementation of regulatory compliant data management tools, CDM team can meet these demands. Additionally, it is becoming mandatory for companies to submit the data electronically. (19)

Clinical trial is intended to find answers to the research question by means of generating data for proving or disproving a hypothesis. The quality of data generated plays an important role in the outcome of the study. (19)

"CDM is the process of collection, cleaning, and management of subject data in compliance with regulatory standards". (19)

The primary objective of CDM processes is to provide high-quality data by keeping the number of errors and missing data as low as possible and gather maximum data for analysis. (19)

To meet this objective, best practices are adopted to ensure that data are complete, reliable, and processed correctly. This has been facilitated by the use of software applications that maintain an audit trail and provide easy identification and resolution of data discrepancies. Sophisticated innovations have enabled CDM to handle large trials and ensure the data quality even in complex trials.(19)

How do we define ‘high-quality’ data? High-quality data should be absolutely accurate and suitable for statistical analysis. These should meet the protocol-specified parameters and comply with the protocol requirements. This implies that in case of a deviation, not meeting the protocol specifications, we may think of excluding the patient from the final database. It should be borne in mind that in some situations, regulatory authorities may be interested in looking at such data.(19)

Similarly, missing data is also a matter of concern for clinical researchers. High-quality data should have minimal or no misses. But most importantly, high-quality data should possess only an arbitrarily ‘acceptable level of variation’ that would not affect the conclusion of the study on statistical analysis. The data should also meet the applicable regulatory requirements specified for data quality.(19)

Classification

The CDMS can be broadly divided into paper-based and electronic data capturing systems.

Paper-based systems

Case report forms are manually filled at site and mailed to the company for which trial is being performed. The data on forms is transferred to the CDMS tool through data entry. The most popular method being double data entry where two different data entry operators enter the data in the system independently and both the entries are compared by the system. In case the entry of a value conflicts, system alerts and a verification can be done manually. Another method is Single Data Entry.(20)

The data in CDMS are then transferred for the data validation. Also, in these systems during validation the data clarification from sites are done through paper forms, which are printed with the problem description and sent to the investigator site and the site responds by answering on forms and mailing them back.(20)

Electronic data capturing systems

In such CDMS the investigators directly uploads the data on CDMS and the data can then be viewed by the data validation staff. Once the data are uploaded by site, data validation team can send the electronic alerts to sites if there are any problems.(20)

Such systems eliminate paper usage in clinical trial validation of data.(20) Case report forms are manually filled at site and mailed to the company for which trial is being performed. The data on forms is transferred to the CDMS tool through data entry. The most popular method being double data entry where two different data entry operators enter the data in the system independently and both the entries are compared by the system. In case the entry of a value conflicts, system alerts and a verification can be done manually. Another method is Single Data Entry.(20)

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Clinical data management

Once the data have been screened for typographical errors, the data can be validated to check for logical errors. An example is a check of the subject's date of birth to ensure that they are within the inclusion criteria for the study. These errors are raised for review to determine if there are errors in the data or if clarifications from the investigator are required.(20)

Another function that the CDMS can perform is the coding of data. Currently, the coding is generally centered around two areas — adverse event terms and medication names. With the variance on the number of references that can be made for adverse event terms or medication names, standard dictionaries of these terms can be loaded into the CDMS. The data items containing the adverse event terms or medication names can be linked to one of these dictionaries. The system can check the data in the CDMS and compare them to the dictionaries. Items that do not match can be flagged for further checking. Some systems allow for the storage of synonyms to allow the system to match common abbreviations and map them to the correct term. As an example, ASA (acetylsalicylic acid) could be mapped to aspirin, a common notation. Popular adverse event dictionaries are MedDRA and WHOART and popular Medication dictionaries are COSTART and WHO Drug Dictionary.(20)

At the end of the clinical trial the data set in the CDMS is extracted and provided to statisticians for further analysis. The analysed data are compiled into clinical study report and sent to the regulatory authorities for approval.

Most of the drug manufacturing companies are using Web-based systems for capturing, managing and reporting clinical data. This not only helps them in faster and more efficient data capture, but also speeds up the process of drug development. Perceptive Informatics, Medidata RAVE and Forte Research Systems' OnCore eClinical are examples of Web-based data capture systems. In such systems, studies can be set up for each drug trial. In-built edit checks help in removing erroneous data. The system can also be connected to other external systems. For example, RAVE can be connected to an IVRS (Interactive Voice Response System) facility to capture data through direct telephonic interviews of patients. (20)

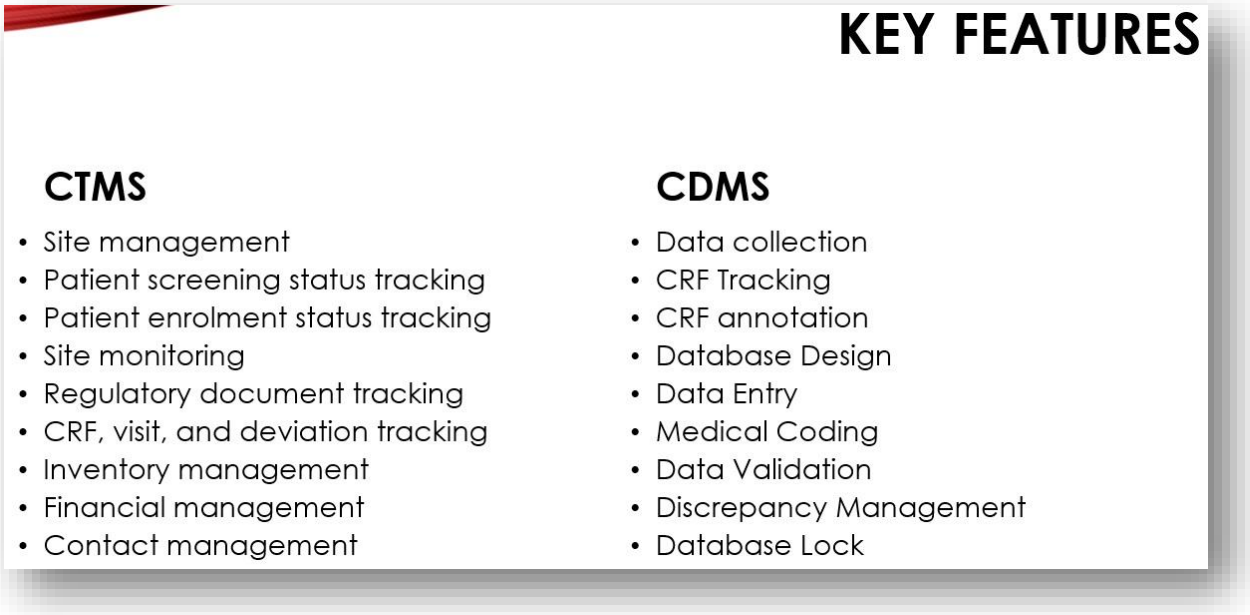


Figure 7: Key feature of CTMS/CDMS

CLINICAL DATA MANAGEMENT REGULATIONS

In regulatory submission studies, maintaining an audit trail of data management activities is of paramount importance. These CDM tools ensure the audit trail and help in the management of discrepancies.(19) Akin to other areas in clinical research, CDM has guidelines and standards that must be followed. Since the pharmaceutical industry relies on the electronically captured data for the evaluation of medicines, there is a need to follow good practices in CDM and maintain standards in electronic data capture. These electronic records have to comply with a Code of Federal Regulations (CFR), 21 CFR Part 11. (19)

This regulation is applicable to records in electronic format that are created, modified, maintained, archived, retrieved, or transmitted. This demands the use of validated systems to ensure accuracy, reliability, and consistency of data with the use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Adequate procedures and controls should be put in place to ensure the integrity, authenticity, and confidentiality of data. If data have to be submitted to regulatory authorities, it should be entered and processed in 21 CFR part 11-compliant systems. Most of the CDM systems available are like this and pharmaceutical companies as well as contract research organizations ensure this compliance.(19)

Society for Clinical Data Management (SCDM) publishes the Good Clinical Data Management Practices (GCDMP) guidelines, a document providing the standards of good practice within CDM. GCDMP was initially published in September 2000 and has undergone several revisions thereafter. The July 2009 version is the currently followed GCDMP document. GCDMP provides guidance on the accepted practices in CDM that are consistent with regulatory practices. Addressed in 20 chapters, it covers the CDM process by highlighting the minimum standards and best practices.(19)

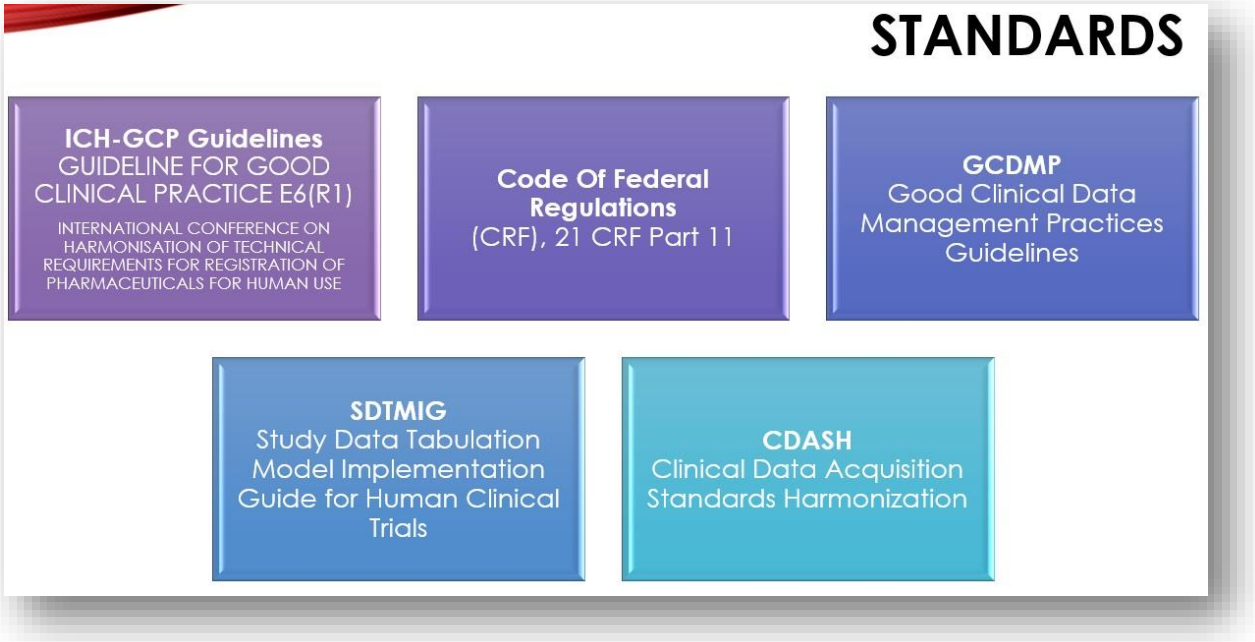


Figure 8: Standards

Clinical Data Interchange Standards Consortium (CDISC), a multidisciplinary non-profit organization, has developed standards to support acquisition, exchange, submission, and archival of clinical research data and metadata. Metadata is the data of the data entered. This includes data about the individual who made the entry or a change in the clinical data, the date and time of entry/change and details of the changes that have been made. Among the standards, two important ones are the Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG) and the Clinical Data Acquisition Standards Harmonization (CDASH) standards, available from the CDISC website (www.cdisc.org). The SDTMIG standard describes the details of model and standard terminologies for the data and serves as a guide to the organization. CDASH v1.1 defines the basic standards for the collection of data in a clinical trial and enlists the basic data information needed from a clinical, regulatory, and scientific perspective.(19)

IMPROVING CLINICAL TRIALS BY IMPLEMENTING INFORMATION TECHNOLOGY (IT)

As clinical trial IT expands in functionality, integration, and ease of use, considerable improvements to clinical development processes and timelines can't be far behind. Or can they? Today's market offers robust software for electronic data capture (EDC) and data mining, Internet-based portals for communication among clinical partners and regulators; and industry-accepted standards for data transmission and submission, yet a lack of adoption of these technologies has contributed to the median time between critical clinical trial milestones, actually increasing since 1997.(20)

In 2004, Merck Capital Ventures (MCV), in conjunction with Science Applications International Corporation (SAIC), embarked on a study of key technology advancements and factors influencing adoption rates. The study identifies current challenges that stall IT acceptance and looks ahead five years to frame a picture of what the IT environment might look like as integrated broad-based electronic solutions are coupled with process change. Together, they are poised to realize more of IT's promised benefits, namely, improved cycle time and data quality, and greater cost effectiveness. (20)

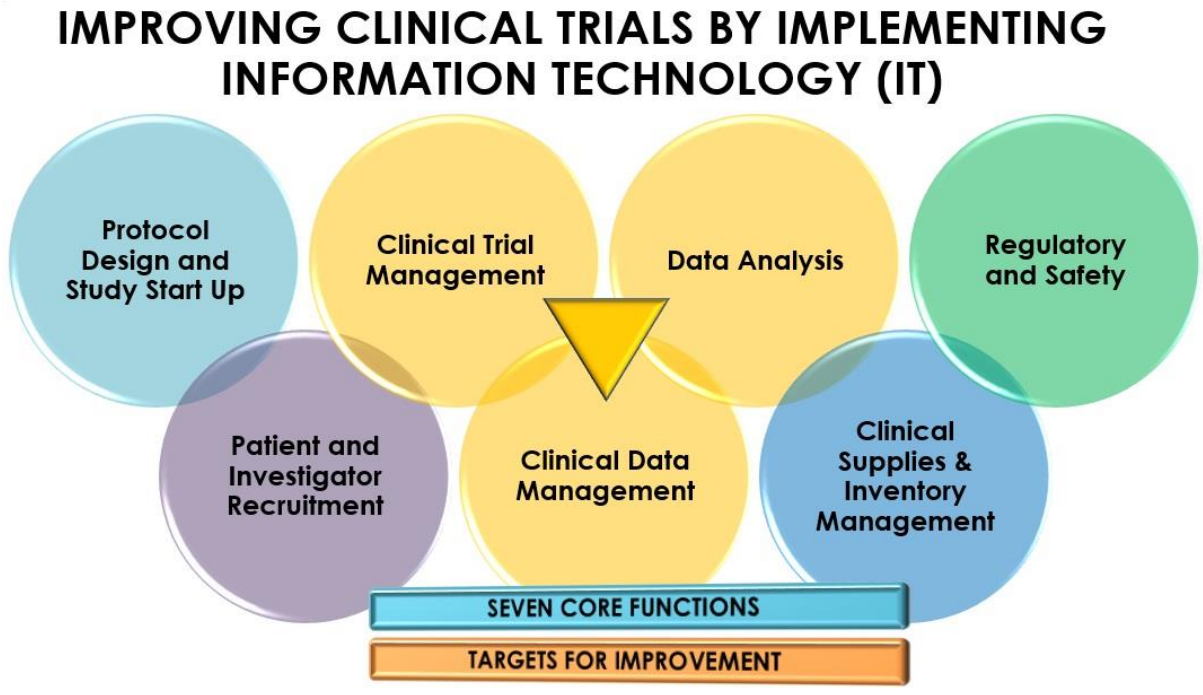


Figure 9: Core Functions

What emerged is a picture of today's IT status from the perspective of seven core functions, ranging from protocol design to regulatory and safety issues (Figure 9). The study revealed, in part, a stubborn adherence to paper-based systems in the face of expansive, searchable, cost-effective solutions, but also a growing acceptance of IT powered by regulatory pressures to improve the efficiency of submissions and adverse event reporting.(20)

To implement the requisite IT solutions successfully within the organization, the research cited process change as elemental. Without it, it is unlikely that new technology meant to improve core function operations will yield expected, significant long-term benefits. In fact, some companies who are achieving short term benefits from new technologies without having changed existing processes now realize they have further entrenched suboptimal business practices, finding it even more difficult to make substantive changes.(20)

Moving Toward the New IT State

It is widely acknowledged that the present state of clinical development remains largely a paper driven process that is cumbersome, time consuming, and costly. Geographically dispersed stakeholders performing internal protocol review via paper copies delay study start-up. Paper-based monitoring and reporting of adverse events slow response time. Response time and quality suffer, and data are not visible to the sponsor in real or near real time. Important metadata cannot be easily generated, and there is no simple way to search data to highlight problematic investigative sites or facilitate decision making early enough to make a difference. And whether trial data are stored electronically or with paper, they tend to be stored in disparate, incompatible systems and formats that complicate data entry, data exchange among stakeholders, query resolution, and data reconciliation during the trial and before database lock.(20)

For many companies, however, change is underway. According to Thomson CenterWatch, in 2004, pharmaceutical sponsors used EDC and/or interactive voice response systems (IVRS) in 44 percent of Phases I - IV clinical trials. This is a quadrupling of the percentage of trials using esolutions as compared to just four years earlier.(20)

Contract research organizations (CROs) used EDC and/or IVRS in a similar volume of trials in 2004 (39 percent) and experienced similar growth in EDC and/or IVRS usage.

The increased use of EDC, however, does not belie the slow adoption of eSource data. Research suggests that eSource is very much in its infancy.

E-solutions success stories are emerging, however. Novartis, for example, reports having implemented EDC in 2001, and now uses EDC in approximately 60 percent of Phase I trials and nearly 100 percent of Phases II and III trials. As a result, the company claims to have reduced the number of contractors in the data management department from 90 to 20, and cut the number of queries to four per 1,000 data points as compared to 51 per thousand for paper based trials. Cost has been slashed to $4.60 per page for EDC vs. $23 per page using paper. The median time for database lock dropped to four days with EDC vs. 10 weeks for paper. The company reports annual savings exceeding $100 million.(20)

What is not known at Novartis, however, is the impact on costs along the entire clinical development process. Focused efforts, such as Novartis's EDC initiative and other impressive examples, demonstrate benefits but overall, victory remains uncertain.

Several sources report that clinical trial durations and costs have not been improving across the industry.

Thomson CenterWatch and Pharmaceutical Research and Manufacturers of America (PhRMA) claim increased spending on clinical development.

In March 2004, the Food and Drug Administration (FDA) presented its current views on deteriorating drug development performance in *Challenge and Opportunity on the Critical Path to New Medical Products*. Data presented in that report indicate that in the last five years, a 55 percent increase in investment is required to launch a new drug, and if biomedical science is to deliver results, there must be a focused effort on improving the medical product development process.(20)

UNDERSTANDING CHALLENGES & OPPORTUNITIES

The promise of IT to help streamline clinical development is perhaps best understood by defining its impact on the seven core functions of clinical development (Figure 9). Those functions figure prominently in the lengthy sequence of events beginning with Investigational new drug (IND) submission and protocol approval, moving to patient enrolment, trial management, database lock, statistical analysis, report writing, and finally, regulatory submission. Each step along the way is fraught with challenges related to inadequate or an absence of technology, or the mixed use of electronic and paper-based methodologies.(20)

One of the core functions, clinical data management, for example, involves collecting information from numerous sources such as investigative sites, CROs, and laboratories. Often, those data are collected in both electronic and paper format, in the absence of collection standards, resulting in multiple trial-specific databases, an array of related systems, and extended time for data reconciliation. These systems, sometimes numbering into the hundreds within a single company, have become ingrained as legacy solutions and loom as huge barriers for change.(20)

Another function, regulatory and safety, attempts the difficult task of integrating data from various functional areas throughout the trial process. Information from distinct databases/systems created for regulatory purposes tend not to be aggregated, limiting data mining capability and ability to respond to regulatory questions or investigate adverse events in a timely manner.(20)

Core Function	Mainstream Process And Technology Characteristics In Three-To-Five Years
Protocol Design	• Wide use of study-specific protocol simulation and adaptive design • Reduced number of amendments via improved decision support systems • Collaboration tools used within project team and with investigator sites • Improved workflow solutions with IRBs and Data Safety Monitoring Boards • Expanded use of Web-based study start-up solutions • Integration with label-driven design initiatives
Patient and Investigator Recruitment	• Earlier input and collaboration with investigator sites to help shape protocol for feasibility of enrolment, as well as assessing site's ability to meet the protocol • Better access to site recruitment figures to alert for slow enrolment and to determine if help is needed to reduce time and cost of enrolment Wider use of site mining, assessment and screening tools • Patient accrual, cost simulation and related monitoring tools • Multi-pronged approach to patient accrual (site database, local advertising, and use of centralized recruiting databases)
Clinical Trial Management	• Near real-time visibility of project status across all studies whether in-sourced or outsourced, active or inactive • Warning systems to identify problems or non-compliance early • Better sponsor access to potential project team resources • Continued outsourcing to CROs, using very defined performance metrics
Clinical Data Management	• eCRF, eCTD and CDISC standards are widely accepted leading to "bridge development" to/from legacy systems • Leveraging existing EDC and electronic patient reported outcomes (ePRO), expanding • eSource collection methods and improving active analysis of trial and clinical data to identify administrative, safety, or efficacy issues early
Data Analysis	• More near real time reporting and analysis occurring during trials (adaptive designs, patient adoption rates, site selection, etc.) • Workflow tools used to streamline and document the process for easy repeatability and increased reuse of statistical programs
Clinical Supplies	• More use of integrated processes and systems for effective manufacturing, inventory, and distribution of small and large orders • Continued use of IVRS and a growing use of Radio Frequency Identification (RFID) technologies to support better tracking and scheduling
Regulatory and Safety	• Faster and more effective participation via Improved cross-functional workflow management and database mining • Use of database mining tools • Shortened durations for document preparation and submissions through use of integrated databases/systems • Global pharmacovigilance function that develops and implements risk management systems, including signal detection and signal management

Table 2: Adoption of e-Solutions Enables Movement towards an Improved Process and Increased Business Value

The MCV/SAIC study suggests that the clinical development landscape may look quite different in three years (Table 2) as technology, business practices, regulatory, and competitive pressures align and integrate to allow e-solutions to address some of the existing challenges. As that happens, many of today's core functions will see real improvement. (20)

It is worth emphasizing that business processes, comprised of workflows, tools, and resources, cannot remain stagnant for these technologies to make a difference. Couple this with regulatory mandates to adopt electronic solutions, and there is no doubt that momentum has started to re-defined industry practice. (20)

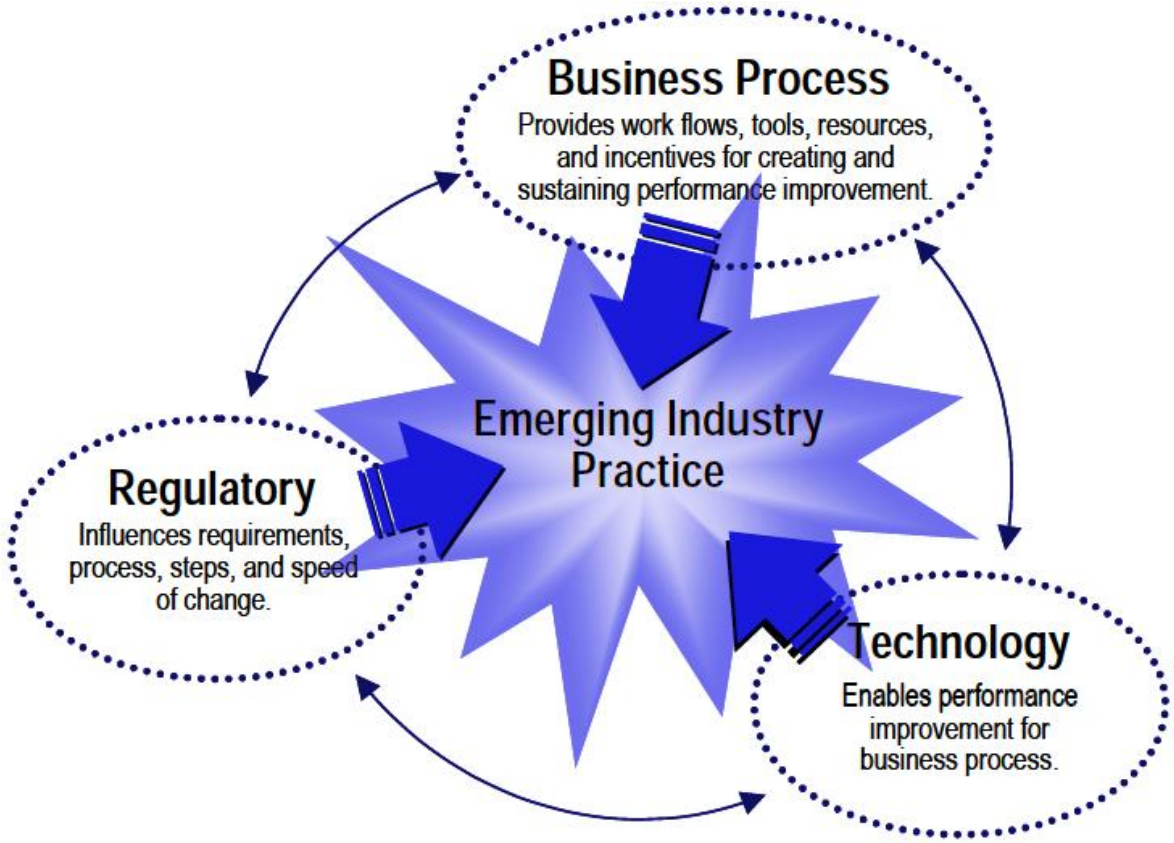


Figure 10: Regulatory, Technology, and Business Practice Alignment

TECHNOLOGY

Technology is the most tangible element of the improved clinical development environment. It is not elusive like business process or open to interpretation like regulatory guidelines. Technology is nuts and bolts—hardware, software, Internet, and intranet. Within its realm is an array of e-tools that enable the process overhaul that the industry needs. They offer greatly expanding functionality, allowing for integration of data and functions, as well as an

infrastructure that will sustain improvements in communication and data exchange into the foreseeable future. (20)

Table 3 illustrates the interdependencies within the clinical development process, and creates a basis for understanding technology's ability to affect the seven core functions. As the table shows, functional applications such as portals, collaboration, decision support tools and work flow management impact six of the seven core functions. Document management and project and portfolio management impact all seven. (20)

It is not surprising that document management solutions affect all seven functions. It is a major challenge for pharmaceutical companies to handle the staggering amount of data generated throughout a trial contained in documents in multiple formats—paper, electronic, and digital—and sometimes requiring updating, or versioning, during the trial.

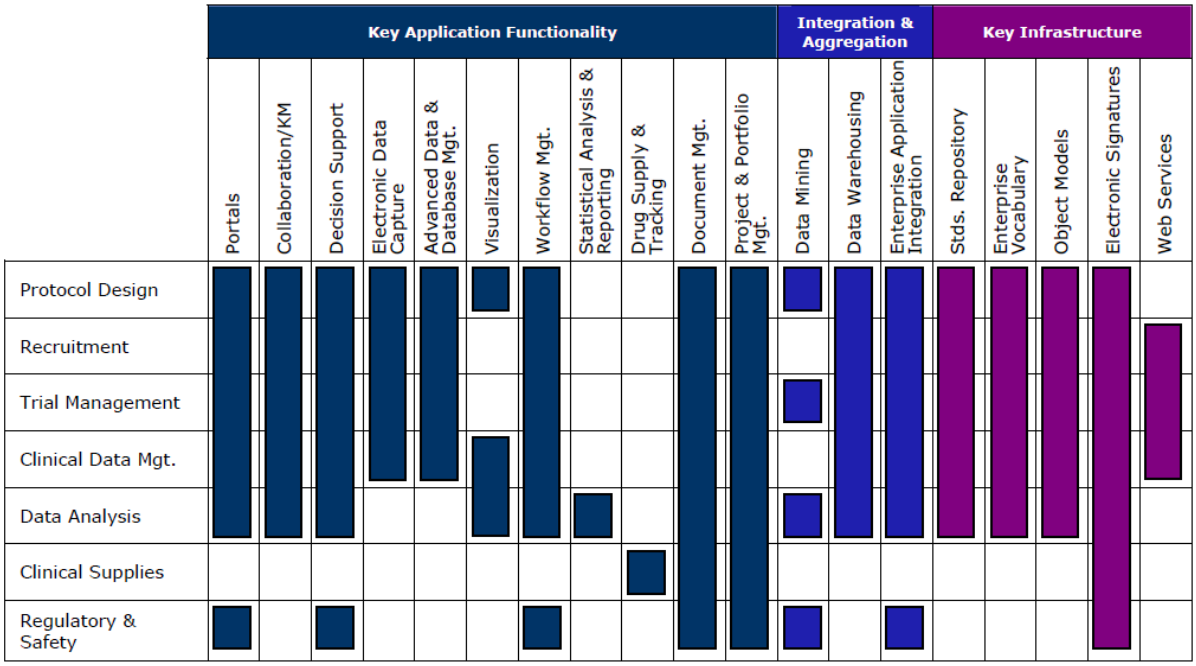


Table 3: Technology Map for Clinical Trials ***Source: SAIC***

In addition to the volume challenge, document management becomes more complex as stakeholders begin to address the changing definition of a document. Two examples of new document formats are: Structured Product Labelling (SPL), a document mark-up standard approved by Health Level Seven (HL7) that describes the content of prescription drug labelling in an extensible mark-up language (XML) document; and the Electronic Common Technical Document (eCTD), an XML-based format defined by the International Conference on Harmonisation (ICH) that renders electronic regulatory submissions valid and enables content

contained with the documents to be searchable and achievable by modules and sections, regardless of version. (20)

Traditional document management applications are not designed to handle these new formats and their features. A robust document management system that provides a common repository with searchable attributes, electronic routing and approval, and life cycle management capabilities such as authoring, version control, and archiving are fundamental enabling technologies. (20)

The Integration and Aggregation section of Table 3 refers to data mining, data warehousing, and enterprise application integration functions.

Integration and aggregation of e-solutions allow sponsors to search and query data across all studies involving a specific product. Similarly, they allow regulatory agencies to search advanced databases and a broad range of data types to identify similar patterns in other drugs with the same chemical structure. This search capability, using visualization tools and adoption of centralized data, metadata, and vocabulary standards, is critical for early detection of potential safety issues and represents a major advance over non-searchable systems in which signals are possibly masked in data stored in multiple formats and locations and coded using different vocabularies. (20)

Search capability, which Table 3 pegs as part of the integration and aggregation function, requires tools from the next component of clinical development—key infrastructure. Successful integration and aggregation involves development of a standards repository and object models to move the process forward. Standards adoption enables the following:

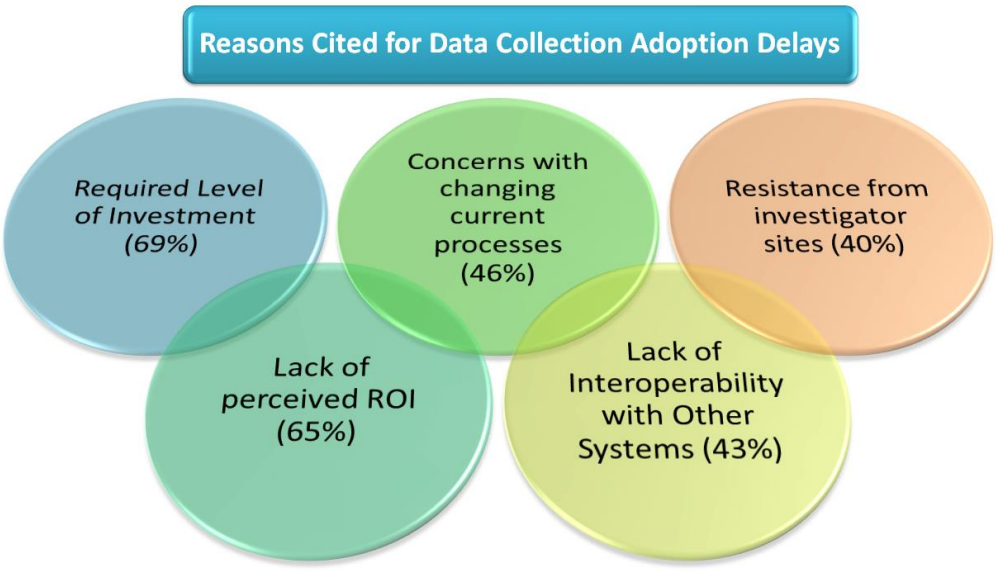
- Standards-based electronic case report forms (eCRFs/CRFs) that decrease time needed for database setup
- Reusable programs that generate standard tables, listings, and datasets, decreasing the time and programming resources required.
- Data being immediately available in the expected format for regulatory submissions (through the use of eCTDs)
- Cross-trial data may be pooled, facilitating data mining and the preparation of Integrated Safety Summary (ISS) and Integrated Summary of Effectiveness (ISE) reports

BUSINESS PROCESSES

Implementing technologies that yield an expected high return on investment requires changes in business processes. These processes are the convergence of tools and resources and revised work practices. They are strongly influenced by regulatory guidelines that are creating specific requirements to which technologies and processes must. (20)

The MCV/SAIC study suggests that over the next three years, forward thinking sponsors and CROs will increasingly respond regulatory and competitive pressures, by taking steps to improve processes that enable greater use of tools to automate data collection, management, and communication among stakeholders; increase adoption of data transmission and submission standards; increase transparency of clinical trial performance; and foster cross-trial efficiencies. (20)

This won't be easy or cheap. Process change that is tantamount to system overhaul in the short term is hardly a realistic goal because of the enormity of the undertaking and the amount of change it would entail. People tend to resist these types of changes, as suggested by draft results of a 2004 CDISC survey in which 46% percent of sponsor respondents cited "concerns about changing current process" as a key reason for data collection technology adoption delays10 (Figure 7). With each acceptance of a new technology, however, the enterprise nudges closer to its goal of system wide solutions leading to greater operational efficiency and quality. (20)



Source: CDISC Draft Results of Research Project, 2004

Figure 11: Reasons Cited for EDC Adoption Delays

Acceptance starts with early adopters of technology promoting its value within the organization. Early adopters are believers or champions for the technology. They are risk takers. Theory suggests that there is a chasm between early adopters and the majority of users.

According to a business text, *Crossing the Chasm*, early adopters seek change whereas the majority of users seek just the opposite—maintenance of the status quo. The majority are pragmatists who accept process change only when they have a compelling reason. Interestingly, the majority eventually becomes the biggest advocates for the technology when they start to believe in it. They spread the word, encouraging other pragmatists to accept it, too.

This technology-acceptance model applies to any industry, but it certainly resonates with the pharmaceutical sector which has been notoriously slow to adopt electronic solutions despite evidence supporting the value of system-wide interoperable technologies. As the industry considers technology adoption, it is important that it not settle for a series of study-by-study or department-by department solutions as this will, at best, yield minimal improvement, and at worse, add to the problem of legacy systems and create even greater costs in clinical development. Companies with cultures that recognize this are likely to reap the benefits of system-wide technology ahead of companies that lag behind. (20)

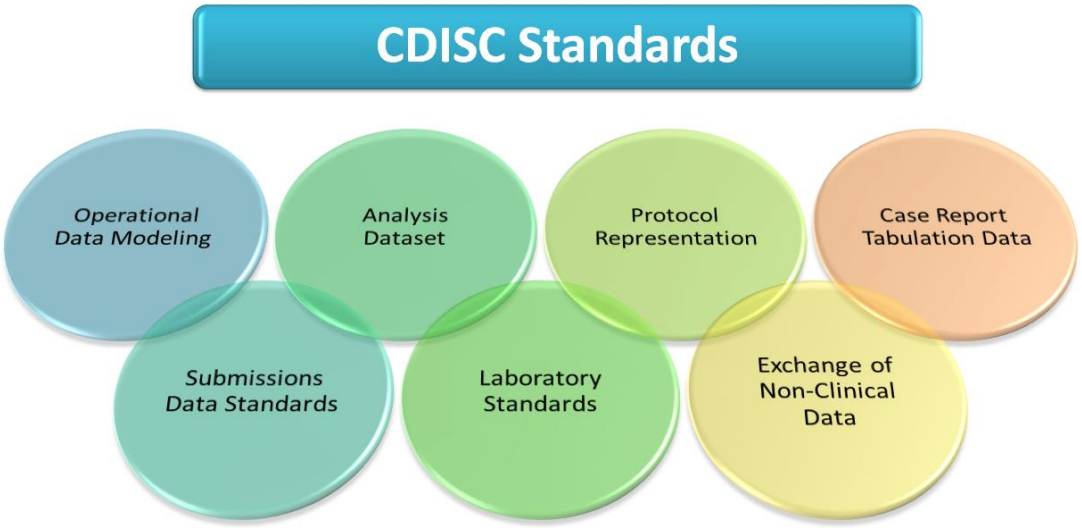
The MCV/SAIC study also reviewed the practice of outsourcing the data management function. While it is too early to draw any conclusions, the initial findings highlight a few issues that are worth considering. For starters, to what extent does a stakeholder allow an outsourced partner to decide which technologies and processes to employ? Restricting them to existing ones limits the potential for benefits and can further entrench existing business practices. Allowing change will introduce risk but may also generate significant benefits. Many thought leaders are concluding that outsourced partners may be best suited for maintaining systems slated for retirement, saving internal resources for new development initiatives. (20)

REGULATORY

More than ever, the most significant factor driving the industry's deployment of IT in clinical trials is the adoption of data-related standards by regulatory agencies. FDA, for example, launched the Data Standards Council to coordinate the evaluation, development, maintenance,

and adoption of health and regulatory data standards to ensure that common data standards are used throughout FDA and that standards are consistent with those used outside the agency. (20)

FDA has provided guidance for submissions using the Study Data Tabulation Model developed by CDISC and has accepted CDISC's Operational Data Model for data interchange and archiving. According to FDA, the standards being developed by CDISC are the centrepiece of the agency's vision for an IT infrastructure that can improve clinical development. (20)



Source: http://www.cdisc.org

Figure 12: CDISC Standards

Further standards are expected to come from the Consolidated Health Informatics Group, an interagency organization in the U.S., and from the HL7 healthcare data standards accredited by the American National Standards Institute and accepted in many nations throughout the world. The industry should also expect increased adoption of Electronic Health Records in U.S. and Europe and continued government and payer pressures for cost and cycle time reductions in drug development. Both will have an impact on the use of IT because both require efficient and effective data exchange and management. (20)

It is identified that three fundamental and interrelated forces driving change in the pharmaceutical industry: technology, business processes, and regulatory guidelines.

Technological advances enable new workflows and promises of interoperability and integration of function, but technology alone has little power to create meaningful change. Successful implementation of electronic solutions requires changes in business processes and an appreciation of how difficult it is for organisations to take those first steps away from paper-based clinical systems that have worked for decades. (20)

Ingrained behaviours are difficult to change, but with the help of internal champions, leading companies are managing to launch new approaches, perhaps incrementally at first, but eventually crossing the chasm to system-wide solutions. The results are indisputable: better quality data, accelerated cycle times, and greater cost efficiencies. Driving the move toward greater use of technology are regulatory forces that are focusing on improved collection, "searchability," transmittal, and storage of data. (20)

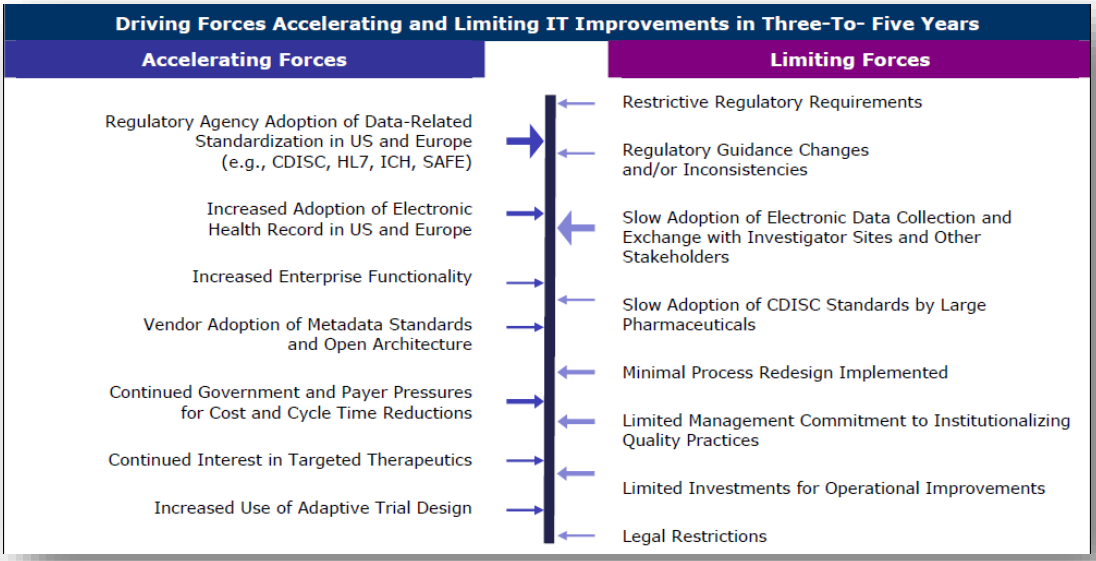


Figure 13: Driving Forces Accelerating and Limiting IT

Figure 13 shows the push-pull of accelerating and limiting forces affecting technology acceptance. Some companies will debate what an ideal solution could look like before making any move forward while others will wait, hoping to find the answer in a regulation or best practices document. (20)

In either case, the result will be unmet expectations and falling further behind. There are no ideal solutions, and reading about best practices and implementing them are very different.

Companies that have set a vision for the future, support a culture for change, and implement processes and projects to move forward are generating tangible rewards, creating learning organizations, and positioning themselves to be industry leaders. (20)

CTMS/CDMS TOOLS

Many software tools are available for data management, and these are called **Clinical Data Management Systems (CDMS)**. In multicentric trials, a CDMS has become essential to handle the huge amount of data. Most of the CDMS used in pharmaceutical companies are commercial, but a few open source tools are available as well. Commonly used CDM tools are **ORACLE CLINICAL, CLINTRIAL, MACRO, RAVE, and eClinical Suite**. In terms of functionality, these software tools are more or less similar and there is no significant advantage of one system over the other. These software tools are expensive and need sophisticated Information Technology infrastructure to function.(19)

Additionally, some multinational pharmaceutical giants use custom-made CDMS tools to suit their operational needs and procedures. Among the open source tools, the most prominent ones are OpenClinica, openCDMS, TrialDB, and PhOSCo. These CDM software are available free of cost and are as good as their commercial counterparts in terms of functionality. These open source software can be downloaded from their respective websites.(19)

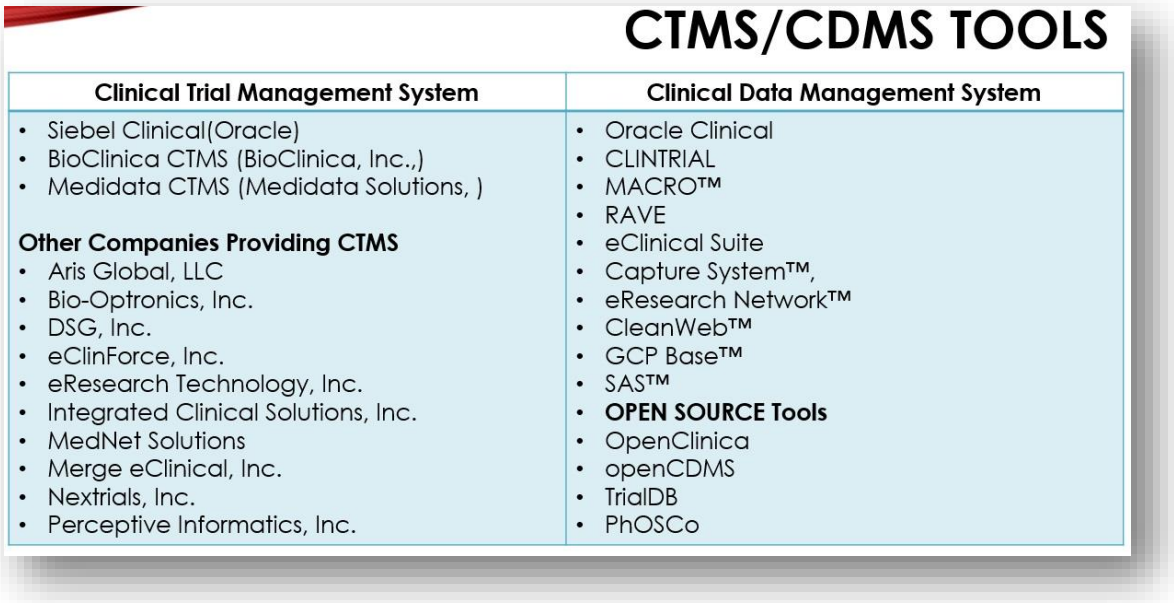


Figure 14: Tools of CTMS/CDMS

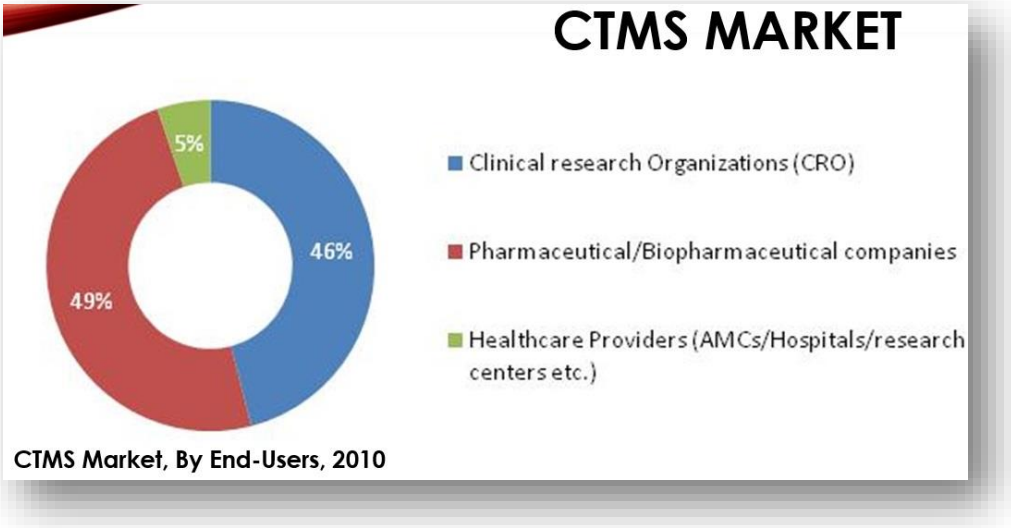
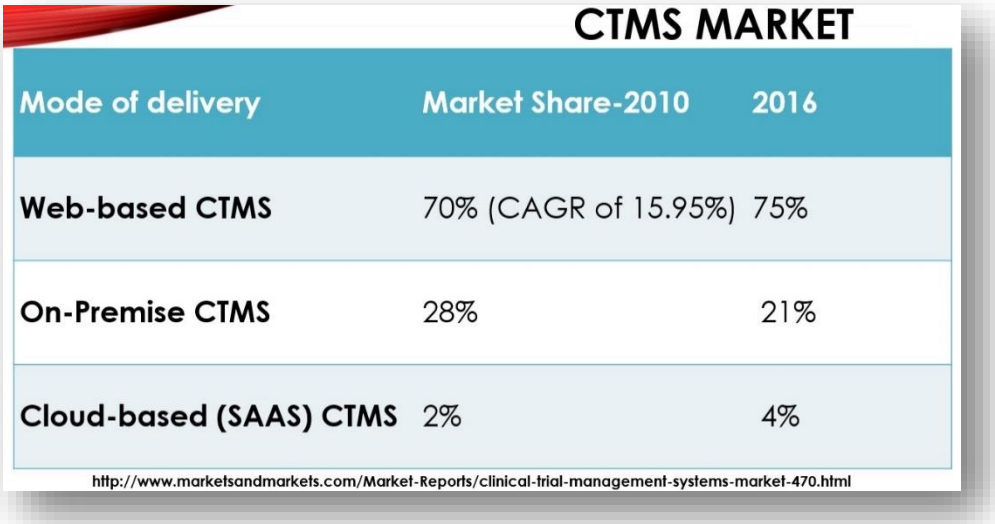


Figure 15: CTMS Market



CHAPTER 7: DISCUSSION

A "Full Service CDMS/CTMS" vendor may be able to provide more support at a much better price.

Every clinical trial requires superior attention to detail whether it is conducted using CDMS/CTMS or paper. In either case, a design must be developed that meets specific protocol and clinical requirements, with the ability to respond to changes with speed and flexibility. What's the most efficient (and easiest) way to conduct trial especially if time and resources are limited.

Many vendors charge more to manage an electronic trial than they will to manage a paper trial, which defeats part of the efficiency of CDMS/CTMS. In effect, sponsors end up paying more for them to learn the system and manage the trial in a way in which they are unaccustomed.

Best option might be a "Full Service CDMS/CTMS" provider that can give all of the speed, quality and cost efficiencies of CDMS/CTMS plus the consulting and support needed to run the entire trial, including customized services to meet specific trial requirements. Of course, relevant therapeutic experience is also critical whether dealing with a CRO or a Full Service CDMS/CTMS vendor.

Speed

One of the benefits of CDMS/CTMS is that, over time, the process becomes more efficient. In most cases, first trial isn't representative of the ultimate speed and efficiency a sponsor can gain. By working with the same solution partner, sponsor can able to build a library of forms and edit checks that speeds your start-up time faster and enhances efficiencies in subsequent trials.

Look for a solution partner that has a track record of on-time, customized delivery. Choose a partner that is strong in the rapid design of intelligent eCRFs, in managing the clinical environment, and performing back-end data analysis and reporting. With a long-term relationship, sponsor can enjoy the efficiencies of CDMS/CTMS the first time, and experience even greater benefits over time.

Choice: freedom and integration rules.

Many CDMS/CTMS vendors offer an integrated eClinical suite (including EDC, Interactive Voice Response (IVR), and eDiary). This provides convenience, and often some level of data integration, but in many cases, individual parts of the suite may not be required for study.

Rather than being forced to utilize their entire suite, sponsor might appreciate a "best of breed" approach, where sponsor can select the best technology for each part of the trial process. For example, integrating a tool or technology sponsor's team is already using and already trained on. Or including a tool that is a better fit for sponsor particular protocol.

Choose an CDMS/CTMS vendor that is flexible and that will enable the integration of whatever solution set sponsor want — without charging more for the privilege.

Data Access

Insist on early access to data, so sponsor can make smarter decisions sooner. One of the greatest advantages of CDMS/CTMS is that you can gain faster (and earlier) access to trial data. Earlier transparent access to data can provide early insight into potential safety issues or trends. It's much better to get bad news on your trial's progress early on — so sponsor can either make changes or shut down the study before wasting time and money, or most importantly, exposing participants to unnecessary interventions.

Data access options vary significantly from one vendor to another. Some make it difficult and costly — charging for each download, or requiring a separate third-party tool to report on or analyse the data. (In that case, sponsor may need to invest in separate training, and pay for additional IT support to maintain a separate application.)

For these reasons, it's best to look for a solution that can give sponsor real-time data visibility regardless of the connectivity options (dial-up or broadband) from clinical sites. Make sure the vendor provides built-in analytics and visualization tools so sponsor don't have to pay for, or maintain them. Finally, demand unlimited access to trial data for little or no extra cost to avoid being hit with extra costs every time sponsor wants to download its trial specific data.

Vendor flexibility

Many CDMS/CTMS vendors force sponsors to re-engineer their approach to fit their processes and technologies. It should be exactly the other way around. CDMS/CTMS solution should tailor itself to meet the requirements of sponsor's protocol, the number of sites sponsor need to support, the demographics of patient population, and the data sets to be analysed.

Having a solution that works for minimizes sponsor frustration and makes for a smoother implementation. Challenge CDMS/CTMS vendor to find ways to add speed and efficiency into every stage of the clinical trial — from forms design, to navigation and workflow, to the design flexibility of eCRFs, adopting the conventions used in a variety of therapeutic areas. Sponsor should have the freedom to design highly customized studies — an option that may not be possible with inflexible systems.

Clean Data

One of the fundamentals of CDMS/CTMS success is getting clean data. When sponsor able to get cleaner data up-front, it requires less back-end cleansing, lowering costs and getting you to submission faster.

CDMS/CTMS vendors often build intelligence into their eCRFs to catch and correct errors in real-time, as well as validate the data early in the process. The sophistication of these edit-check capabilities varies widely, however, vendor should be able to provide any combination of instant validation checks customized to sponsor specific needs. These checks highlight and flag users against entering inappropriate data.

Automated and manual queries (either system or user generated) are also helpful in speeding data entry and guiding users to accurately enter the data that is needed.

Overall, this kind of intelligence only available through CDMS/CTMS can minimize data entry errors and user frustration leading to fewer data discrepancies and requiring less back-end data cleansing. The net result is cleaner data throughout the study, higher overall quality, and faster time from last data in until final database lock.

Ease of Use

Like any other technology, the easier the CDMS/CTMS system is to use for both the sponsor and the site user, the greater the productivity that is unleashed across every part of the process.

Ease of use at the end-user sites and clinics minimizes the training required and encourages faster adoption of the technology.

Ongoing study visualization tools, such as dashboards, easy-to-use patient-to-patient navigation and easy access to commonly used tools (such as reports) should be key parts of the CDMS/CTMS vendor's offering.

In addition, features such as customizable workflows for multiple sites and customizable user permissions can minimize training time at the site and during data analysis. The ability of users to work productively off-line (in other words, not connected to a network whether offsite at a clinic or traveling on an airplane) can also increase productivity in significant ways.

The best way to ensure ease of use: take a test drive, and get references from sites that currently use the system. Finally, make sure vendor listens well to your specific user needs and is willing to make adjustments to work the way sponsor want to work.

Controlling costs

One of the main things to consider with CDMS/CTMS as with any other service is managing costs or, more specifically, being able to predict the costs sponsor will incur. Be wary of vendors who provide a low initial bid and then escalate costs as the trial progresses — adding separate charges for data transfers, study changes, training, live data, or live query listings. These unexpected "extras" can add up quickly leaving sponsor with significant cost overruns. Instead, it's best to negotiate a fixed price before the trial begins —agreeing to the cost for all processes, products and services upfront.

Be sure vendor understands what's included in the cost of the study and what are considered add-on charges. This will make it easier for sponsor to run trial — with less paperwork, fewer approval cycles, and fewer headaches.

MARKET PLAYERS

As of today, India has witnessed different types of players venturing into the traditional method of the data management business. Some of them are full-fledged CROs starting separate data management units, some of them are IT / ITES companies (22) planning to support the data management business in terms of providing data management solutions and some are pharmaceutical companies setting up biometrics and data management operations solely on their own or through partnership.(22) Others are entrepreneurs not related pharma or CRO or IT business, but joining the fray looking at the prospects of the business.(22)

MARKET PLAYERS

Pharmaceutical Companies	Contract Research Organisations (CROs)	IT/ITES Companies
Johnson & Johnson	Quintiles	Accenture
Pfizer	Covance	Wipro
GlaxoSmithKline	Pharmaceutical Product Development (PPD)	Intel
Roche	Charles River Laboratories (CRL)	Satyam
Sanofi-Aventis	ICON Clinical (ICON)	Cognizant
Novartis	Parexel	IBM
AstraZeneca	MDS	Oracle
Abbott Laboratories	Kendle	TCS
Merck	PharmaNet Development (PharmaNet)	Infosys
Wyeth	PRA International	Medidata
Bristol-Myers Squibb		BioClinica
Eli Lilly		

Figure 16: CDMS/CTMS Players

While Pfizer has their own data management unit, they are also using the FTE and FSP model and using the services of SIRO ClinPharm and Cognizant for their data management initiatives. Other local and global pharma companies in India either have their own data management unit or outsource locally to a CRO or other local service provider for full or part of their data management and statistical analysis related tasks.

DESCRIPTION OF MAJOR PRODUCT USED (ITS KEY FEATURES & BENEFITS)

ORACLE HEALTH SCIENCES

1. **Oracle Clinical (Clinical Data Management System)**

Oracle clinical provides sponsors and CROS a single application and infrastructure for EDC and CDMS built on proven technology for scalability. Benefits include:

- improved site productivity and operational effectiveness
- lower cost of ownership
- technology enablement to maximize the it investment

More than 250 pharmaceutical, biotechnology, medical device, and contract research organizations have depend on Oracle Clinical to conduct more than 10,000 clinical trials, making it a proven clinical research solution. Oracle Clinical's operational effectiveness, lower cost of ownership and technology enablement increase ROI with each study. (23)

Oracle Clinical and Oracle Remote Data Capture provide a single application and infrastructure for electronic data capture and clinical data management, while leveraging the renowned Oracle database. Oracle Clinical enables management of all clinical trial data in a single system, improving accuracy, visibility, and data integrity. (23)

2. SIEBEL CLINICAL TRIAL MANAGEMENT SYSTEM (ORACLE)

Oracle's Siebel Clinical Trial Management System offers a new and innovative approach to managing clinical trials. The approach focuses on strengthening relationships with trial participants, especially investigators and subjects, by using Siebel customer relationship management (CRM) software solutions.(24)

KEY BENEFITS

- Centralized trial management database
- Global trial support: multi-lingual, multicurrency, and multiple time zones
- Improved investigator relationships
- Increased clinical research associate (CRA) productivity
- Improving Clinical Trial Efficiency with Optimized Processes
- Ability to Design Complex and Adaptive Trials
- Robust Global Trial Management
- Reduce project risk and cost with Oracle Consulting Services

3. CLEARTRIAL PLAN AND SOURCE CLOUD SERVICE PRODUCTS

Oracle Health Sciences ClearTrial Plan and Source Cloud Service products leverage embedded industry intelligence and clinical knowledge to optimize clinical study planning and sourcing and rationalize the deployment of R&D spending. The cloud-based software enables to compress study timelines while reducing costs; accelerate the delivery of accurate, defensible, and achievable budgets; and reduce outsourcing cycle times while increasing negotiation leverage.

Product Overview

The activity-based planning methodology in Oracle Health Sciences ClearTrial Plan and Source Cloud Service products encompasses the detailed tasks and costs required to plan a clinical study—enabling to build study plans and Request for Proposal (RFP) documents from the bottom up simply by entering clinical assumptions. Delivered as cloud-based, software as a service (SaaS) applications, Oracle Health Sciences ClearTrial Plan and Source

Cloud Service products offer industry-proven algorithms for more than 200 therapeutic indications; specific clinical development data and clinical research organization (CRO) labor rates for 90 countries; and detailed clinical, cost, and resource reports.

Business Value

Biopharmaceutical, medical device, and diagnostic companies are faced with the increasing complexity and cost of bringing new therapies to market. Traditional methods of using spreadsheets, generic planning software, and ad hoc planning processes have led to lengthy planning and contracting cycles, inaccurate budgets, and high variances between planned budgets and actual costs.

Oracle Health Sciences ClearTrial Plan and Source Cloud Service products provide with visibility into the operational and financial plan for a study as well as the ability to quickly model new scenarios as per clinical assumptions, business requirements, or outsourcing needs change. The result is more efficient and accurate clinical study planning, budgeting, outsourcing, and execution—reducing study cost and risk and optimizing deployment of R&D capital.

Key Features

Oracle Health Sciences ClearTrial Plan and Source Cloud Service products leverage the following key features to deliver results:

- **Embedded global clinical intelligence.** Industry-proven algorithms are provided for more than 200 therapeutic indications, with specific clinical development data and CRO labor rates for 90 countries.
- **Activity-based planning methodology.** More than 140 documented study assumptions enable to build study plans from the bottom up reflecting development goals and processes.
- **Centralized repository for operational data.** Clinical plans reside in a secure database, accessible via a secure Web connection to any number of users across the globe.
- **Fast "what-if" scenario planning.** In just minutes, we are able to assess multiple clinical development strategies, including any combination of service providers and any outsourcing model.
- **Rapid time to value.** Delivered as a cloud-based application, with an interface designed by clinical professionals, the software begins delivering business value in less than a week.

Key Benefits

Oracle Health Sciences ClearTrial Plan and Source Cloud Service products deliver the following benefits:

- **Accuracy.** Oracle Health Sciences ClearTrial Plan and Source Cloud Service products have been benchmarked by leading biopharmaceutical and medical device companies to deliver 95 to 99 percent accuracy when compared with actual study costs.
- **Speed.** In minutes, it can create comprehensive clinical project operational plans as well as detailed study budgets and RFP documents—directly driven from clinical assumptions. Accelerate outsourcing contract closure time by up to 75 percent while maintaining study objectives.
- **Efficiency.** Oracle Health Sciences ClearTrial Plan and Source Cloud Service products allow to optimize studies for maximum efficiency, shortening timelines and reducing costs while maintaining the achievability of the study.
- **Consistency.** The output of a set of clinical assumptions is the same no matter who builds the plan, while an audit trail makes it easy to identify the most up-to-date version of the operational plan and budget—as well any modifications.
- **Flexibility.** The software supports all clinical development methodologies and outsourcing strategies, as well as your own business processes. Oracle Health Sciences ClearTrial Plan and Source Cloud Service products also provide a common platform for sponsors and

CROs to conduct more-collaborative development—putting the focus on study feasibility and business value.

LIMITATION

- Quantitative analysis cannot be done in limited timeframe
- No Historic data available
- Most of the data are proprietary and not accessible

CHAPTER 8: CONCLUSION

REAL-TIME SHARING AND COLLABORATION

One of the overriding problems with using file shares and paper document copies is the lack of efficient access to the data. Directory structures are often very complex or randomly created. It is not unusual for one user to check out a document for edit, which another user from editing the same document or even a completely different document. Users are prevented from using their time effectively as wait for the file to be available. Or worse, data slips through.

A common example would the embarrassment caused when the sponsor suddenly calls for a report on the status of something. The person who deals with that area isn't in the office and the sponsor is desperate for the report. Or worse yet, that person is busy with other tasks and taking the time to create the report can have an adverse effect on the other work. By having a CTMS system, a CRO can allow the sponsor to retrieve their own reports without involving anyone else. The sponsor gets what it wants instantly, and the CRO does not need to tie up valuable resources.

FEWER RESOURCES REQUIRED

Use of a CTMS can streamline processes and functions. By simplifying tasks that are traditionally very time and resource consuming, a CTMS can lead to fewer people being required. The costs savings this brings in can be passed on to a sponsor. As a result, a CRO is more economical to sponsors and becomes more sought-after in the marketplace.

INSTANT STATUS AND TRACKING

In addition to the collaboration issues mentioned previously, using a CTMS can give a CRO real-time access not only for its administrators and project managers who require data to be readily available and clear, but also for other users (such as management or executives) and even the sponsor without needing to generate reports or give the users access to raw data. They can see or order scheduled snapshots of relevant areas.

FORCES STANDARD, OPERATING PROCEDURES TO BE ADHERED TO

Because the CTMS system would be configured at the start of a trial with the rules and requirements for that trial, it can enforce adherence to procedures. This might appear to be cumbersome and inflexible. The advantage is that it enables the trial to be more easily

conducted according to the trial protocol and company rules. This in turn helps to prevent any hint of impropriety or making a trial invalid over small but repeated procedural irregularities that could have been easily avoided.

QUICKLY HIGHLIGHTS DEFICIENCIES AND PRE-EMPTS POTENTIAL PROBLEMS

The ability to clearly define and report on each functional area according to the rules of the trial make it possible both to be quickly reactive to problems that arise, and often to be proactive in dealing with problems before they can happen. There is no need to sift through huge spread-sheets or go to multiple locations looking for potential problems. A CTMS can help to identify out-of-variance visits, deficient regulatory documents, and unresolved monitoring issues, as well as to help renew documents before they expire.

STOPS 'TO-BE-DONE' ITEMS SLIPPING THROUGH – BOTH INTERNAL AND MONITORING

The system never forgets! Even the most organized people sometimes make mistakes and forget to make a note of something, or do so in haste and not in the "usual place," which can lead to forgetting or misplacing the item or task. The system will not! It keeps track of every task either according to the protocol, company SOPs, or individual rules for the clinical trial. The system tracks tirelessly and will continue to remind users that resolution is required until a task is completed.

FEWER ERRORS IN BOTH DATA AND PROCEDURES

The culmination of all the above points is that fewer errors occur due to the CTMS:

- stopping items from slipping through the cracks.
- enforcing procedures.
- only adding the data once, always in the same place and in real-time.
- prompting for issue resolution.

Decisions are made based on more accurate and up-to-date data, without having to hunt for and then piece together the complete picture. Complex and in-depth reconciliation is therefore needed less and less.

CHAPTER 9: RECOMMENDATION

CTMS/CDMS BRINGS BENEFITS THAT HELPS A CRO IN TERMS OF

TIME SAVINGS

End the frustration of constantly creating and chasing down reports, reconciliation, duplicating tasks, finding data, analysing data to see if it is in compliance with the rules, and looking for problems. These issues can all be easily and seamlessly addressed within a CTMS. As a result, a CRO can have a decreased workload and a smaller, more focused team. Not only does *Time equal Money*, but *Workload is directly proportional to Stress* and hence productivity.

COMPETITIVE EDGE

A decrease in the time and cost of performing duties can result in an increase in profits and a decrease in costs quoted to sponsors. This can make a CRO more competitive in the marketplace. The CRO can advertise its use of a CTMS system as a bonus in addition to its services. This demonstrates the CRO's investment in the success of a sponsor's trial, as well as the regulatory and communication benefits for them.

COMPLIANCE

Regulations cover an increasingly broad spectrum of clinical research operations, resulting in heightened concerns regarding full accountability and compliance. To avoid the risks involved with altering or substituting a page that a hardcopy report affords, a CTMS makes it possible to capture every alteration of data in audit trails and often with a comment as to why the data was amended. This provides greater transparency into a situation that might have occurred years before and maybe even made by employees who have since left the company.

This makes the results of the trial more credible to the regulatory bodies and the sponsor.

CONTROL

With the ability to bring functions back in-house, a CTMS enables a CRO to more easily control operations and adherence to procedures. By having the data readily available and clearly presented, managers can make better decisions regarding the running of a trial. This in turn leads to a more favourable and efficient outcome and a lower administration cost for the trial.

COMMUNICATIONS AND ALERTS

A CTMS provides easy and automated notification when key tasks need to be performed. Users can make approvals but don't have to constantly police the whole study system for such important tasks or issues. The system alerts them instead. All users see the same real-time information. It doesn't matter who's in the office or not, or who's got a document buried on their desk. A CTMS provides direct access to reports for management and executives. It is no longer necessary to customize data for a specific request; all information is available on-demand.

MANPOWER SAVINGS

Perform more study tasks with fewer people.

INTANGIBLE COST SAVINGS

CROs can also realize some less tangible but nonetheless very real cost savings.

- **Decreased errors**: It is very hard to put a price on how much errors cost, as there are so many factors involved in their reconciliation. It is however, considerable.
- **Less stressful work environment**: By smoothing out the extremes in the burden of task spectrum (mindless at one end and very complex at the other), a CTMS can improve employee productivity and reduce staff turnover, with downstream effects of reduced training costs and improved continuity in trial management and practices.
- **Benefits to marketing**: A CRO can market its company as using a CTMS in order to highlight its mature, state-of-the-art clinical trial management infrastructure. By providing cutting-edge capabilities to sponsors, the CRO obtains a competitive advantage.

There are many substantial savings to be made, both directly and indirectly, from the use of a CTMS. Direct savings in administration costs alone could pay for the CTMS within one trial. By improving overall efficiency, a CTMS can help reduce product timelines and meet trial deadlines. With the pressures that characterize the current state of the drug development industry, a CRO would be wise to consider implementing CTMS software to assist it in delivering successful outcomes with its clinical trials. The CRO just may wonder how it ever managed without it.

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CASE STUDY 1

COMPARITIVE STUDY OF PAPER MEDICAL RECORDS & ELECTRONIC MEDICAL RECORDS

International Institute of Health Management Research, New Delhi

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INTRODUCTION

Medical record is a systematized way of storing the required data, information and other relevant documents with the objective of making easy availability of necessary data at the time of its need. It is a systematic documentation of a single patient's long-term individual medical history and care. These records are intensely personal documents and so there are many ethical and legal issues surrounding them.

Medical record consists of information like name of patient, address, age, sex, occupation, disease, modes of diagnosis and recommendations made the by the concerned doctor in course of undergoing treatment This information contained in the medical record allows health care providers to provide continuity of care to individual patients. It helps patients to acquire the right and apt treatment. Moreover, it acts as a tool for the doctor who is looking into the patient.

IMPORTANCE

- Systematic Medical records play a vital role in the field of delivering proper health services to the people. These are vital in both hospitals & public health.
- A caution is necessarily taken, in course of treatment as there must be a name and signature of concerned doctor who is involved in the treatment of any patient in medical record.
- A patient may derive a right treatment after quick and meaningful diagnosis of disease.
- It contributes towards knowing the health condition of people, ailment stricken areas, cause and effects of disease.
- Helps in attaining the health related information through thorough check up of such medical records.
- The government can avail such records in the direction of making short as well as long term health strategies.
- Through the study of medical record, preventive measures are to be timely adopted in order to save people from being ill.
- The epidemics and other disease tending to spread can conveniently be well informed in time.

Now a days there is a big revolution in the country due to the advancement in Information technology. These days there is not even a single area left without the use of the information

technology. Since healthcare industry is a very big industry & vital for the people so it needs to be both effective & efficient. Thus, the use of information technology is very important .This need prompted the integration of information technology with the healthcare industry. When Information technology is used for the recording of patient information like demographic details ,medical history , current medications etc. then it is called as EMR (electronic medical records).Electronic medical record (EMR) is nothing but a medical record of a patient in digital form. The digital information is usually stored in a database and is accessible from everywhere via a network. This concept is mostly used in foreign countries. Usually in INDIA patient's medical information is normally recorded on paper written in a patient's record at every doctor's office the patient has visited or in the medical chart hanging at the foot of a patient's hospital bed. This is paper medical record (PMR). Here in this case study the comparison is done between paper medical records & electronic medical records.

METHODOLOGY

The EMR is used in foreign countries like U.S.A. It is just being introduced in INDIA so the methodology used is observational & discussion method. The information is collected primarily by observation of the software and making a comparison between paper medical records & electronic medical records. Discussion is done with the subject matter expert. Focus points of discussion are:

- Disadvantages of PMR
- Advantages & EMR over PMR
- Disadvantages of EMR.

Also some information is collected using secondary data sources.

OBSERVATION

Through observation some comparison is made between PMR &EMR.

In PMR patient is identified by name, medical record number & other identifier.	In EMR patient can be identified by any identifier i.e. Name, SSN, Date of birth, phone number.
In PMR Progress notes might be produced by dictation, free handwriting or form completion.	In EMR progress notes are produced as the visit is produced.
A PMR consists of office or progress notes in chronological sequence. These are browsed by literally flipping through pages, until the desired entry is located.	An EMR stores progress notes and provides quick access by date of visit, provider and the ability to browse by diagnosis and prescription.
In PMR prescription is written on paper. It is manually checked for interactions & allergies. It is then taken by the patient to the pharmacy .It takes time & can also result in errors.	In EMR prescription is written in the system. It is checked for interactions & allergies by the system & then it is sent to the pharmacy by the system directly where it is verified & drug is dispensed. There are rare chances of errors.
In PMR Laboratory and radiology reports are filed in more or less chronological order. Access to specific entries in it is not much efficient as it is with the progress notes.	An EMR stores reports in any number of ways to provide rapid access and quick reference. In this access to specific lab results or other patient reports is highly efficient and useable. Also we can have access to scanned images, direct lab result posting & even to on-line lab information applications.
In PMR if a paper chart is filed correctly in the medical records system, a staff member must go to the stacks of charts, use some quick identifier code, locate the correct last name. The first name is located and confirmed & then the chart is pulled by inserting a placeholder in order to 1) make re-filing easier and 2) record where the chart is headed. There are chances of the chart getting lost.	In EMR the records remain exactly in the place where they should be. An electronic chart is never lost out or misfiled. Also electronic record may be accessed from any point in a healthcare facility that has access to medical records.

DISCUSSION

On the thorough discussion with the SME on the medical records we got to know about the advantages & disadvantages of PMR & EMR. We had a thorough discussion about the disadvantages of PMR.Only on knowing about the disadvantages one can agree well to the benefits & use of EMR.

DISADVANTAGES OF PMR

1. Needs lot of space for storage.

2. No centralization of records & collection of records is a tedious task..

3. More chances of medical errors caused by poor legibility on paper forms.

4. Less in efficiency as compared to EMR.

5. Data cannot be easily exchanged or transferred.

6. They are not eco-friendly.

The idea of EMRs itself started about 40 years ago. However, there is surprisingly a strong resistance against the use of EMRs. Through lots of discussion with the SME we got to know about the pros & cons of using EMR.

ADVANTAGES OF EMR

1. There are increasing storage capabilities for longer periods of time.
2. Is accessible from remote sites to many people at the same time.
3. Retrieval of the information is almost immediate.
4. The record is continuously updated and is available concurrently for use everywhere.
5. Information is immediately accessible at any unit workstation whenever it is needed.
6. The EMR can also provide medical alerts and reminders.
7. EMR systems have some built in intelligence capabilities, such as recognizing abnormal lab results, or potential life threatening drug interactions.
8. EMR supports accountable autonomy, collecting and disseminating information to assist the medical professional in decision making.

9. An EMR is that it allows for customized views of information relevant to the needs of various specialties.
10. EMR can provide information to improve risk management and assessment outcomes.
11. An EMR can increase the productivity of healthcare workers and decrease medical errors due to illegible notes.
12. Financially, the EMR will provide more accurate billing information and will allow the providers of care to submit their claims electronically, therefore receiving payment quicker.
13. Patient does not have to continue to provide the same information over and over again.
14. Increases patient privacy.
15. Eliminate repetitive manual tasks.

Not only it just has advantages. It has some disadvantages too.

DISADVANTAGES OF EMR

1. Start-up cost is high.
2. Lack of Technical knowledge.
3. Inability of the provider to adapt.
4. Usability is a major issue.
5. Placement of hardware is an issue.
6. Crashing of computer & loss of data.
7. Change in workflow of the department after the implementation of an EMR.
8. Lack of standardized terminology, system architecture, and indexing.
9. Lack of flexibility and lack of capacity for the diverse requirements of the different healthcare disciplines.

RECOMMENDATIONS

1. The robust back up methods, sophisticated protection mechanisms & advanced data recovery methods should be developed.
2. Decisions regarding the portability of the equipment must also be considered.
3. Documentation forms must be revised in order to accommodate the changes in the workflow.

4. Development of standard language is required.
5. A unique health identifier must also be developed.
6. Well planned training must be given to the end users.

CONCLUSION

With the above discussion & observation we can see that the advantages of the EMR are more than the disadvantages of EMR. Its implementation can help in improving the efficiency & effectiveness of the healthcare industry. The most important concern is that the users need to be trained properly & given enough time to get adapted to it. Data security is also a concern for the implementation & use of EMR. If these two concerns are taken care properly with relevant solution to the problem the implementation of EMR can be a success. This can prove to be a boom for the nation.