ELECTRONIC SOLUTIONS FOR CLINICAL RESEARCH STUDIES

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ABSTRACT

Electronic solutions can provide efficient and effective ways to handle specialized requirements of clinical research mandated by the requirements of the Code of Federal Regulations. However, the industry has been a slow adopter of such solutions in part due to lack of standardization. Compatibility and standardization issues and the complexity of the electronic systems have contributed to the slowing of the marketing of novel products. This paper surveys widely accepted electronic solutions in clinical research, discusses their advantages and disadvantages along with implications to practitioners.

Keywords: Electronic solutions; clinical research; regulation; standardization.

INTRODUCTION

Clinical research is conducted as a requirement of federal regulations mandated by the Food and Drug Administration (FDA) and is necessary, as proven by history [1], to protect the public from undue risk. In general, the regulations for drugs fall under the title 21 Code of Federal Regulations (CFR) part 312 and for devices 21 CFR 812 along with the FDA's guidance document [2], International Conference on Harmonization recommendations, Declaration of Helsinki, and Belmont Report. All of the regulations are in place to protect research subjects from undue risk and to describe the guidelines for ethical treatment of those subjects. Additionally, the regulations and guidelines help define general and specific requirements for all of the players involved in clinical research–clinical investigators, companies sponsoring the studies, clinical sites, and institutional review boards.

CLINICAL STUDIES PROCESS

In order to apply for FDA approval to commercially market a drug or device for sale in the US, pre-clinical and clinical studies are required, which are described below:

Pre-Clinical Studies

The research phase can be a long duration before a product even comes close to being used in humans. Generally referred to as basic research, the early part of a drug or device lifecycle is at the bench side where scientists experiment and analyze results from testing thousands of compounds or devices. Emerging from the laboratory is no small feat. When a compound or device makes it to pre-clinical studies, there is cause for celebration. This accomplishment can be the result of three or more years of hard work (refer to Figure 1).

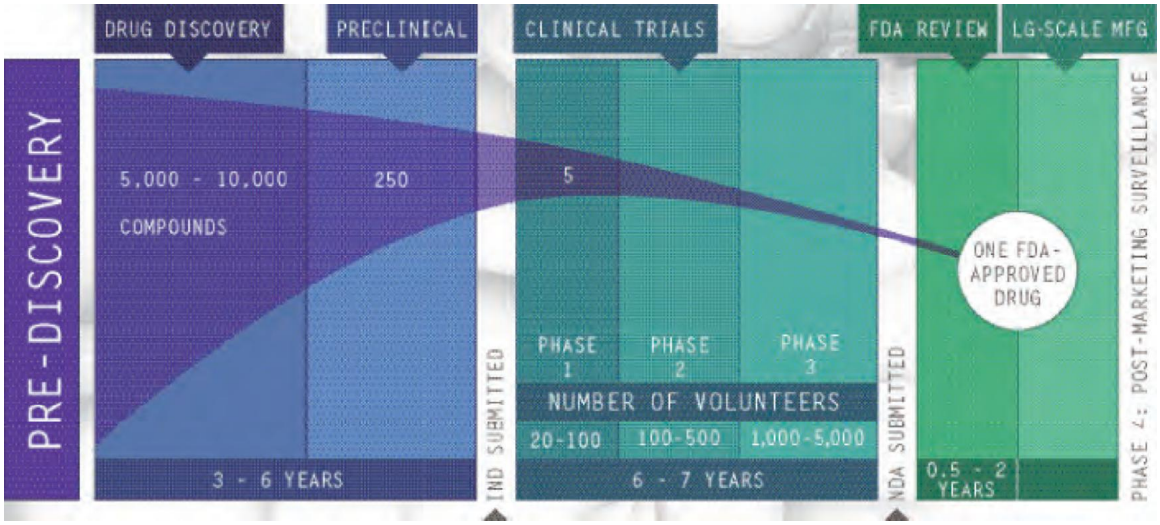

Figure 1: Pharmaceutical Timeline [3]

Before any human testing can occur, pre-clinical studies must be conducted to test the potential toxicity, mutagenicity, and carcinogenicity of a product. The studies revolve around determining how a product is absorbed, distributed, metabolized, and excreted, collectively referred to as ADME studies. In pre-clinical studies, the mode of administration, rate, and site of drug uptake are examined in animals. The purpose of pre-clinical studies is to determine the relative toxicity and reasonable safety for use in humans.

Phase I – IV studies

Before a company can begin testing a new drug in humans, an Investigational New Drug (IND) application must be filed with the FDA. The analogous submission for a device is called an Investigational Device Exemption (IDE). The purpose of the IND/IDE is to ensure that study participants will not face any undue risk from use of the drug or device. The IND/IDE contains data from the pre-clinical studies and should confirm the relative safety for use. If no news from the FDA arrives after 30 days of the IND or IDE submission, the company can proceed with their planned clinical study.

Phase I studies evaluate the safety of a drug or device, generally in about 20 to 100 healthy volunteers, in some cases (oncology studies), patients with the target disease may be enrolled in Phase I studies. These studies can also be referred to as First In Man (FIM) studies. The primary goal of Phase I studies is to evaluate the safety and tolerability of the drug and to protect the safety of study participants; however, a secondary goal could be to evaluate the clinical efficacy of the product. Any unanticipated adverse effects are closely monitored at this stage. Data from clinical studies are collected on case report forms (CRF), which are forms, designed to capture the information required or specified in a study protocol. The protocol is a working plan for the study, which specifies what types of data need to be collected, in addition to the general conduct of the study, study objectives and endpoints.

Phase II studies evaluate the safety and efficacy of a drug or device usually in about 100 – 500 patients with the targeted disease. Additionally, the dose of the drug can be determined at this phase using dose-response studies. Also, the study design may use a placebo as a comparator and the search for any additional indications for use (additional diseases that may be treatable with the product) are evaluated.

If the product makes it successfully through Phase II studies, then the pivotal or Phase III study may begin. Phase III studies evaluate the safety and efficacy of a drug or device in about 500 – 1,000+ patients with the target disease. The dose of the drug and manufacturing scale up should be well defined and documented at this phase. The study is pivotal in the sense that the study should be able to prove to the FDA that the drug or device is safe and effective for the intended indication for use.

At the completion of Phase III studies, ideally the clinical endpoints and study objectives have been met and an enormous amount of data has been gathered to support the safety and efficacy of the product. This supporting documentation, along with other product specifications or data (such as, chemistry manufacturing and controls, toxicity studies, labeling information, clinical microbiology studies, and human clinical data), will be submitted to the FDA in a New Drug Application (NDA). The equivalent submission for devices is the Pre-Market Approval (PMA) process.

The purpose of the NDA is to provide sufficient information for the FDA to be able to determine the following:

1. To determine whether the product is safe and effective for its intended use
2. Whether the product's labeling is appropriate and contains the proper information, and
3. Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity [4].

Incredibly, on average, only 20% of drugs (1 out of 5) entering the clinical study phase will eventually result in an approved product (refer to Figure 1). After roughly 10-15 years of hard work, it can be heartbreaking to see a product fail at the pivotal study. Approximately $800 – $1.0 billion [5] are spent on the research and development of a new drug, it is no wonder why prescription drugs can be so expensive.

Phase IV studies or post-marketing studies are voluntarily conducted by companies to gather additional safety data. When the FDA requests additional post-market safety data, the studies are referred to as post-approval studies and are mandatory. These types of studies are generally referred to as Phase IV studies and can have thousands or tens of thousands of patients enrolled.

ELECTRONIC SOLUTIONS

As described previously, each of the phases of clinical research studies can have thousands of data points collected. Multiple time points may be collected from patient's lab results or clinical exams to endpoint outcomes throughout the study resulting in a massive amount of data. It seems reasonable to expect that those involved in clinical research would eagerly embrace the use of electronic data collection, analysis, and tracking; however, in general, the clinical research industry has been a slow adopter of electronic solutions. The use of paper as a source of data collection in clinical studies still lingers even though the industry acknowledges the importance of utilizing electronic solutions [6]. Only companies that have the cash, training plan, and resources to implement an electronic solution can manage to take on the task of bringing an electronic system online.

Clinical research is one of the most heavily regulated industries and, as such, there are certain requirements that electronic systems must comply with according to the FDA's regulations (21 CFR Part 11 Electronic Records) [7]. Not only are there user and cost barriers to entry using electronic systems, but also there are also regulatory hurdles to overcome. Part of the slow adoption can also be attributed to a lack of standardization in the systems used. Emerging recently as the industry standard is the Clinical Data Interchange Standards Consortium (CDISC), which is a "global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata." The stated mission of CDISC is as follows: "The

CDISC mission is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare." [8]
With the advent of a widely accepted industry standard, compatibility issues can be minimized as vendors start to adopt these norms. From a Project Management perspective, the use of standardized electronic systems could mitigate the risk of losing data during transfers from system to system. The standards should help to stimulate the creation of compatible systems that will provide encouragement to smaller companies to start adopting the use of these electronic solutions. Summarized below are some of the most widely used electronic solutions.

ELECTRONIC SOLUTIONS TYPES

There are many types of solutions that are available to the clinical researcher, from electronic data capture to voice recognition systems and suites of management and data solutions. Often, vendors promoting the product will claim the simplicity of implementation; however, the installation and configuration of these systems can be quite complex.

Electronic Data Capture

Even though only 5-10% of clinical studies use Electronic Data Capture (EDC) it is widely recognized as the wave of the future in clinical research data collection. EDC is typically a web-based application that allows the end users (clinical research sites, such as hospitals, doctors offices, and clinics) to enter clinical data while the companies sponsoring the research can remotely review the data in real time. EDC systems have a Graphical User Interface for ease of use, a validation or audit trail element, and a reporting piece for data analysis. Even though not widely implemented, the use of EDC can speed the data entry and analysis by allowing the data to be reviewed and queried as entered.
Benefits of using EDC are elimination of illegible data, reduction in time spent monitoring data at a clinical site, and the ability to use automated query generation and data clarification. In a paper system, the data has to be transcribed by another person and entered into a company's clinical database. This step is removed when using an EDC system, avoiding potential user entry errors. The EDC has built in reporting and data tracking that can be utilized by the Project Manager to monitor the progress of the study. Additionally, the ability to quickly download the data during and at the end of the study can be a great advantage especially at a time when speed to market is an ever-present issue.
The disadvantages of using an EDC system are user ability and acceptance, site and company equipment limitations, system limitations, and initial cost. From experience, there can also be issues with connectivity and access. For instance, if the EDC vendor server goes down, that means the entire study is without use of data entry, tracking or analysis. This can be very problematic and cause delays in data or adverse event reporting; vendor issues can delay even the completion of a study. Another issue with vendors of EDC systems can be time zone factors.

Interactive Voice Response System

Interactive Voice Response Systems (IVRS) are typically used to randomize or enroll patients into clinical studies; however, it can also be used as a drug inventory management and subject recruitment tool. This type of system is commonly used even with studies that utilize paper case report forms. An advantage of this system is its relative ease of use for the layperson and equipment demands are low (touch pad telephone). Disadvantages are the limited scope of this system. There are other more effective management tools that will be evaluated in the next sections. Eventually, as more clinical sites

and companies adopt higher technology solutions, more comprehensive electronic systems will replace the need for IVRS.

CONCLUSION

With technological advances, the collection and analysis of large amounts of data can be greatly improved through the use of electronic solutions. To date, efforts to improve the efficiency of data management in the clinical research industry through electronic solutions has been fractious. Numerous hardware and software providers are attempting to develop products for the industry, but no clear standard has emerged until recently. With the advent of CDISC, standards have been developed that the industry can move forward with to speed the adoption of electronic solutions.

With the deep pockets of the federal government and additional players entering the market, the costs of implementing a full suite of electronic solutions for clinical research will decrease and acceptance and adoption of the solutions will increase.

From a project management perspective, a full suite of interfaced applications would be a-dream-come-true effect. Having the ability to run reports with real time data at the fingertips is a benefit when you add to that the ability to interface with clinical trial management systems, clinical document control, and budgeting applications then it becomes a very powerful tool. Who says we live in a country of no new frontiers? It seems plausible that clinical research is still an open frontier when it comes to applications and their interface with software suites. Clearly the future of electronic solutions in clinical research is coming soon.

REFERENCES

A full set of references is available upon request from Arvinder Loomba, San Jose State University.