Paperless clinical trials: Myth or reality?

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ABSTRACT

There is an urgent need to expedite the time-to-market for new drugs and to make the approval process simpler. But clinical trials are a complex process and the increased complexity leads to decreased efficiency. Hence, pharmaceutical organizations want to move toward a more technology-driven clinical trial process for recording, analyzing, reporting, archiving, etc. In recent times, the progress has certainly been made in developing paperless systems that improve data capture and management. The adaptation of paperless processes may require major changes to existing procedures. But this is in the best interests of these organizations to remain competitive because a paperless clinical trial would lead to a consistent and streamlined framework. Moreover, all major regulatory authorities also advocate adoption of paperless trial. But challenges still remain toward implementation of paperless clinical trial process.

KEY WORDS: Clinical trial, clinical trial management systems, electronic data capture, electronic health records

Introduction

Handling clinical trial data can be an enormous and complicated enterprise, and such a critical procedure can often be stalled by ineffective methods. Managing the monumental amounts of paper in clinical trials can be very expensive. Hence, the pharmaceutical industry is willing to shift from the complicated and expensive paper-based clinical trials.[1-3] As a matter of fact, many pharmaceutical companies have an inclination toward paperless clinical trials, and they have launched products and software to boost this. Recently, a pilot study conducted by the collaboration of Bristol-Myers Squibb and National Cancer Institute in 2010 reported that use of digital signatures and cloud depository of electronic records can decrease the costs of clinical trials. In this study, interoperable digital identity authorizations were employed that allowed them to authenticate electronic records with a validated digital signature. These records were kept in the “cloud” (virtual network of data pools) provided by third parties and retrieved through Internet-based links. Thus, the data were safe and at the same time could be expeditiously retrieved. Combining such technologies with clinical trial management systems (CTMS), electronic consenting, electronic health records (EHR), and electronic data capture (EDC) can enhance the shift toward paperless clinical trials.[2] Could the long-awaited move toward paperless clinical trials really get a boost from digital identities, digital signatures, cloud depository of electronic records, and other technological advances? Let us first discuss about technological components which are making the dream of paperless clinical trial a reality and then explore the challenges in implementing paperless trials.

Clinical Trial Management Systems

A CTMS is software employed by pharmaceutical companies and Contract Research Organization (CRO) to support and supervise the planning, execution and reporting of clinical trials. CTMS keep track of deadlines of regulatory filings.[14] A CTMS also augments trial supply consumption based on patient enrollment.[15] In short, we can say that CTMS is software to track and manage the clinical trial. Clinical trials are steadily moving toward Internet-based CTMS. But the effect of these processes on the volume of paper in a trial is not much mainly because this is software that manages the trial. But the adoption of...
CTMS and EDC (discussed below) will be integral in enhancing and transforming the data collection and management aspects of a trial. Its adoption shows the trend toward going electronic in a bid to improve inefficiencies and cut costs.\(^\text{[15]}\)

Electronic Consenting

Informed consents are a very important component of the clinical trial. Informed consents are moral and statutory duties that need to be performed before enrollment of subjects in clinical trials. Informed consent forms (ICFs) have circumstantially increased in length and due to this subject and study personnel require an excessive time to appropriately review the ICF. This often creates obstacles in enrollment of adequate numbers of subjects in the clinical trial. Failure to enroll sufficient number of research participants in an adequate period of time basically magnifies the cost of clinical trials.\(^\text{[9]}\) Similarly interrelated are the authorizations needed for utilizing subject’s protected healthcare information for research purpose. Mostly, ICFs and privacy authorizations are collected using paper-based processes. Taking informed consents electronically lead to a distinct set of data that can be connected to clinical data to increase the enrollment of subjects in the clinical trial.\(^\text{[9]}\)

With electronic consenting subjects can open the hyperlinks for further elucidation on vocabulary or even find out a segment of the ICF narrated in the language of their own. Furthermore, each subject’s queries, as well as the time spent on each page, can be traced, giving investigators the conviction that ICF are being thoroughly read and thoughtfully comprehended. Thus, taking informed consents electronically augments study enrollment in a logical timeline. In addition, electronic consenting can serve as the first alert to the sponsor that a subject is going to participate in the study. Amalgamation of electronic consenting with EDC systems (discussed below) can give a holistic picture of the subject-related processes right from informed consent till study completion.\(^\text{[9]}\)

In addition, electronic consenting also gives useful risk alleviation platform for study sponsors. The use of electronic medium generates an option for enriching the informed consent procedure with audiovisual or other multimedia contents.\(^\text{[9]}\) Thus, the electronic consenting process can do a higher quality work in enlightening likely subjects of the hazards and gains of being a participant in the clinical trial. The current upsurge in the number of global trials also emphasizes the importance of electronic consenting.\(^\text{[9]}\)

Sanderson et al., 2013 described a novel method of taking informed consents electronically. They reported that by ameliorating the capability to trace probable study participants, we can enhance enrollment into clinical trials. In addition, we can improve study participants learning by introducing multimedia contents to informed consent processes.\(^\text{[10]}\) Obeid et al., 2013 also illustrate the blueprint and pilot of a new and elaborate mechanism for electronic consenting process and privacy authorizations. They tested the use of touch screen technology on a mobile tablet computing gadgets in the consenting process.\(^\text{[9]}\)

Electronic Data Capture

Electronic data capture is a streamlined system to efficiently compile, clean, substantiate, and supervise the data. It is a platform for real-time, authorization-based passage to clinical trial data. The notion that EDC was just about an electronic version of case report form or eCRF has taken a quantum leap as it is being recognized that EDC is about the assimilation of diversified operations related to the clinical trial.\(^\text{[11]}\) With EDC technology, the error management can be done in very short duration, and paper utilization and paper amount can be abbreviated.\(^\text{[12]}\) In addition, protocol breaches and data outliers can be recognized at the time of data entry itself. With EDC, the time to start the study, database clean-up and database lock can be abridged notably.\(^\text{[13]}\) Moreover, EDC can give similar data accuracy compared to paper-based methods. Indeed, EDC already is helping to decrease the time and money spent in performing clinical trials EDC solutions apparently have the highest influence so far on the load of paper used in clinical trials, as they deals with the critical functions of collecting, managing, and validating data.\(^\text{[14‑18]}\)

Expedition of data collation by EDC is also instrumental in implementing the adaptive clinical trials. EDC permits data integration from diverse origins in near real-time scenario making the supervision of adaptive design clinical trials very easy. Integration would remove unnecessary processes and would thus decrease expenditures too. EDC also corroborates the appraisal of clinical endpoints which helps to accomplish accelerated, unprejudiced, and consolidated decision about strenuously updated data.\(^\text{[11]}\) But it has been argued that EDC software must be compliant with regulatory norms, technically robust, adaptable, and durable.\(^\text{[12,17]}\)

Electronic Health Records

The EHR also called as electronic medical record (EMR) or electronic patient record (EPR) has turned out to be one of the most significant advances in healthcare which has facilitated the electronic repository and reciprocation of health-care dossier. Although these are not really related to clinical trials but show the trend toward going electronic particularly in the developed countries. More importantly, the idea of mining EHR data to drive clinical trial recruitment has gained impetus in recent years in developed countries. EDC permits the clinical research personnel’s to enter and scrutinize the data in real-time while the EHR permits end-users at a healthcare institution to do the same. Although these two technologies are very identical in both configuration and operation, acceptance of these technologies is somewhat lackadaisical.\(^\text{[19]}\) The possibility of EHRs benefitting the clinical research has received minimal contemplation till now. With appropriate indemnity, the EHR could open the door for integration between healthcare and clinical research settings, leading to up gradations in the purview and competence of clinical research. The probable research gains encompass the systematic generation of hypotheses for research to conducting clinical research based only on the EHR. With EHR, the specifics such as widespread presence and variation of illnesses in the community could be collated effortlessly which can assist in designing the research studies. The patient-related segment of the EHR could be used either to know the desire of the potential subjects to take part in research or it can help in appraising potential research participants about existing trial. Electronic triggers from EHR could signal an investigator of a subject’s suitability for an existing trial. The informed consent processes could be managed methodically under full clinical data, and research guidance by the help of EHR.\(^\text{[20]}\) Coorevits et al.
believe that contemporary quality-assured EHRs, linked with a mechanism that backs semantic interoperability would safeguard confidentiality and provide various clinical research tools. Thus, clinical research can be expeditious, of superior virtue with a lesser budget.\textsuperscript{[130]}

Although embracing of the EHR and EDC technology is still in shambles, there is no doubt at all that EDC and the EHR can give paradigm shift to the clinical trial methodology. With perfectly devised EHR and EDC solutions, we get a suitable and economical way for entering data, managing data, and accomplishing study reports.\textsuperscript{[21]}

There has been an ongoing debate on harmonizing the EHR and EDC to speed up the research. But from the clinical research standpoint, still there is no practical amalgamation of EHR and EDC.\textsuperscript{[21,22]}

Moreover, proprietorship, consent, and access to health data are major issues in using EHR data for clinical trial recruitment. It is often argued that data mining and secondary use of health data needs the informed consent of the patient. Moreover, patient’s opinion should be sought in the decisions about the access and proprietorship of EHR data.\textsuperscript{[23]}

**Cloud Storage of Electronic Documents**

As an alternative to conventional paper-based procedures, the data could be generated, disseminated, and stockpiled on an internet platform provided by an extensive, implicit, safe and discreet system of servers known as “cloud.” In a cloud-based platform, clinical research data interchange and the related communique with sites and other outside clients becomes swift and secure. With the reliable computerized communication of information, the study start-up process can be appreciably expedited because study sites can have instant online access to the study related documents. When trial data are kept on a safe cloud-based solution, the sponsor or CRO can do the real-time tracking of each trial site’s progress. The “cloud” becomes spot where clinical trial personnel, procedures, and data interface for real-time delivery of clinical trial operations.

The cloud-based solution also limits the access to only approved users and ensures an audit trail through its security safeguards. Thus, we get an additional wall of security and control that is simply not viable in the manual, paper-based processes.\textsuperscript{[24-26]}

A cloud-based solution is also user-friendly, and one does not need to be specialists to use this.\textsuperscript{[27]}

**Digital Signatures**

Procedures and operations involved in clinical research operations generate a huge amount of paperwork. This can result in accountability concerns and difficulty in managing amendments, approvals, and monitoring changes. By implementing digital signatures into their operations, pharmaceutical organizations can handle these hassles conveniently.\textsuperscript{[28]}

The electronic solution can ameliorate the task of conducting a clinical trial by giving us the capacity to digitally sign a lawful document. The operating system for digital signatures can be instated in various digital devices. A digital signature is a specific pattern that special software generates by implementing an arithmetical corollary and an encoded clue to a memo or dossier. In the United States (US), 21 Code of Federal Regulations (CFR) part 11 has emphasized the importance of digital signature.\textsuperscript{[130,29]}

The specific pattern substantiates both the dossier author’s concreteness and the preservation of the virtue of the dossier during its transference. Thus, more advanced user validation is possible using digital signatures. If embraced as a virtuous and lawful practice for clinical trials, digital signatures would save a lot of time. In addition, digital signatures generate a permanent electronic trail which is very important in cases of the regulatory audit. It also substantially reduces the costs of storing paper-based documents.\textsuperscript{[30]}

**Internet as a Vehicle for Conducting Clinical Trials**

This is not the part of the paperless trial per se rather this is a different way of doing trials particularly trials that require repeated subject contact. But the prospect of carrying out clinical trials exclusively on an online platform is a tempting but relatively uncharted domain. The Internet has huge potential as a tool for conducting trials due to its tremendous reach among the masses and its technological potentials. This may be particularly relevant to clinical trial designs that require repeated subject contact.\textsuperscript{[31]}

McAlindon et al. suggest that the web-based trial strategy is most appropriate when the intervention is safe, the disease can be affirmed by remote means, and the result can be measured by using electronically transmissible innovations. With these caveats, the web-based trial method gives the option of conducting clinical trials rapidly and proficiently.\textsuperscript{[32]}

**Challenges in Implementing Paperless Trials**

A major challenge is the low usage of CTMSs, the inadequacy of the expertise to exchange and use the information between CTMSs and EHRs. Consequently, tools are required to simplify the exchange and use the information between EHRs and CTMSs. Some interesting developments have occurred recently, which include the establishment of key research data sections that can be interchanged easily between EHRs and CTMSs such as processes for transacting data, data elements and terminology, scenarios, and workflow integration during the accessing of information and data security and retention issues.

Another is the creation of the EHR Clinical Research Functional Profile which is a collaborative effort to expand and adapt the functionality of EHR and associated systems, networks, and processes to support clinical research and gives a description of practical necessities for utilizing EHR data for clinical trial. Another key development is the creation of Retrieve Form for Data Capture by the Clinical Data Interchange Standards Consortium (CDISC) for inattentively filling up a research form using EHR data with minimum interference to the whole system.

The Partnership to Advance Clinical Electronic Research (PACeR) launched by the Hospital Association of New York State, brings together leadership from major New York-based healthcare systems, hospitals, research organizations, and pharmaceutical companies to create and sustain efficient processes to more quickly and easily match patients with clinical trials. This was initiated in 2011 to authorize the alternate use of EHR data for the clinical trial. The adoption of electronic medical records by health care providers has resulted in emerging databases of information that will be tremendously valuable to medical research. PACeR’s ultimate goal is to link these data resources with clinical trials in a manner that greatly improves research and patient outcomes while ensuring data and privacy protections. In addition, The American Medical Informatics Association issued a categorization of alternate use of EHR
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There is also a requirement to harmonize EHR and EDC to lessen the recurrence of data entry by study personnel in two systems. But there are enormous roadblocks that prevail in making such enterprises financially viable because software packages and data standards usually differ, and also there are considerable worries about data confidentiality.11

Thus, another bottleneck is standards. During the trial period, the standards reduce the amount of queries generated, improve data quality, and reduce the time to lock the database. These standards allow the regulatory bodies to run their review-tools on the submitted data, leading to far fewer questions about the data structure and, therefore, shorter review cycles with faster approval. In addition, data standards simplify the data transfer between data providers and data receivers while the trial is ongoing. There is a consensus that the promotion of proven global standards has a vital role to play in sustaining efficient and economic data sharing. The CDISC has been working on establishing standards. CDISC is also active in projects promoting harmonization of EDC with EHR. In the healthcare discipline, the HL7 organization creates standards for the interchange, management, and harmonization of electronic clinical data. HL7 Standards facilitates the development of information system interoperability specifications that facilitate the required exchange of information between parties involved in the registration of clinical trials and the reporting of results for registered trials. CDISC found the Biomedical Research Integrated Domain Group (BRIDG) in 2004 to integrate the tools from available clinical trials information systems into a harmonized prototype. The BRIDG prototype delineated with the HL7 development framework elucidates standard operations, responsibilities, hallmarks, and actions for the usual practice in standard clinical trials. This is important because BRIDG model was developed to provide an overarching model that could readily be understood by clinical research domain experts and would provide a semantic basis for harmonization among standards within the clinical research domain and between biomedical/clinical research and healthcare. It could be employed as a key data standard for administering the system in clinical trials and for creating clinical trial software.34

Furthermore, the utilization of patient records for research use strengthens the worries about privacy and institutional accountability. Institutional review boards must justify the need for patient record confidentiality vis-à-vis an investigator’s requirement to investigate prospective clinical uses. The Health Insurance Portability and Accountability Act were executed by the US Food and Drug Administration (FDA) to reduce the mishandling of confidential data and to regulate the access to patient records.35

**Viewpoint of Major Regulatory Authorities**

The US FDA elaborated the requirement to modernize clinical trials as part of its Critical Path Initiative. The European Medicines Agency is also working on ways to modernize clinical trials. Since EDC has turned into a legitimate option to paper-based trials, sponsors confront the test of making clinical trial instruments compliant with various regulations. The principles of good clinical practice (GCP), which mandate the standards of data ethics in paper-based system, must apply similarly to EDC. The growth and utilization of computerized frameworks for clinical trials are explicitly controlled. In 1997 the 21 CFR part 11 was issued in the US to address predicaments for quality, confidentiality and truthfulness of data that the US FDA will acknowledge as identical to paper records. Thus, electronic records need to follow a CFR, 21 CFR Part 11. This regulation is relevant for records in electronic format.36 The 21 CFR Part 11 rules state that computerized systems ought to meet all administrative necessities with the same quality as paper-based data collections and must use electronic signatures as the legitimate equivalent of individual handwritten signatures.37 Subsequently, the US FDA published Guidance for computerized systems used in clinical trials in 1999 that was restructured and reissued in 2007. In Europe, the necessities for e-CRF are incorporated in the GCP guidelines of the European Medicines Agency.38,39

**Paperless Clinical Trial and Developing Countries**

Parekh states that the use of electronic systems for clinical trials in developing countries such as India has been affected by a number of practical problems. Many doctors working in developing countries prefer things in the more traditional way. As electronic solutions are relatively new to the clinical trial industry in developing countries, healthcare professionals are not very well-versed with it, and they may need proper training in operating the systems. Moreover, organizations have reported that electronic solutions have actually increased costs in some regions. One of the main reasons for this is the cost of adopting electronic technology which requires an updated infrastructure and facilities. The lack of Information Technology infrastructure support for electronic solutions is another area of concern for many developing countries. Above all the regulatory authorities in developing countries need more thorough understanding of electronic solutions and may require more time to get acquainted with it. As mentioned before, US FDA has taken initiative to modernize clinical trials. In addition, the European Medicines Agency is also working on ways to modernize clinical trials. Regulatory bodies from developing countries should also take such initiative for the successful adaptation of electronic solutions in clinical trials.37

**Conclusions**

In recent times, the progress has certainly been made in developing paperless systems that improve data capture and management. The adaptation of paperless processes may require major changes to existing procedures. Even though it may require major changes to existing procedures, this is in the best interests of these organizations to remain competitive because a paperless clinical trial would lead to a consistent and streamlined framework. All major regulatory authorities also advocate adoption of paperless trial; hence the adoption of this framework should be the goal of any organizations involved in filing of clinical trial data to these bodies.8,40 But in such a strictly regulated process, there are many stumbling blocks. For instance, EDC technologies have to be impregnable, adaptable and durable. Moreover, interoperability is a major concern. It is imperative that various systems can work together without an extremely grueling and time-taking integration process. In order
to attain specialized and meaningful interoperability, prevailing standards (e.g., CDISC) have to be integrated and linked.\(^{[11-43]}\)

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**Conflicts of Interest**

This article is the author's personal opinion and is not the opinion or policy of his employer.

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