Seminars in Oncology Nursing 000 (2020) 151005

Contents lists available at ScienceDirect

Seminars in Oncology Nursing

journal homepage: https://www.journals.elsevier.com/seminars-in-oncology-nursing

Oncology Research: Clinical Trial Management Systems, Electronic Medical Record, and Artificial Intelligence

Candida Barlow, MSN, CTN, RN*

Bio-Optronics, Rochester, NY

ARTICLE INFO

Key Words:
Clinical Trial Management System (CTMS)
integration
electronic medical record (EMR)
artificial intelligence (AI)
research team
research nurse

ABSTRACT

Objective: To discuss the implications of electronic systems and regulations regarding the use of electronic systems implemented during the conduct of a clinical trial and identify the impact of such platforms on oncology nurses' responsible for providing care to the research participant.
Data Sources: Peer-reviewed journal articles, internet, book chapters, and white papers.
Conclusion: Electronic systems are being increasingly used in the conduct of clinical research. Electronic systems enable the capability to streamline data transfer, remote enrollment capabilities, greater transparency of the trial conduct, improved research documentation, and clearer audit trails. The oncology nurse is at the center of implementation of electronic systems to support the conduct of clinical research and enables safe and effective care to the research participant.
Implications for Nursing Practice: Oncology nurses are vital to the successful outcome of clinical research studies and are key members of the clinical research team. Electronic systems move beyond traditional data collection in clinical trials with multiple benefits. Such systems may enhance the successful completion and adherence of the clinical trial and maintain the safety of the individual consented to research trial.

Introduction

Over the past 10 years there has been increased complexity in the clinical research protocol and higher associated costs to conduct clinical trials. Because of the increasing number of clinical trials available internationally, this means an increased workload for research teams and investigators.[1] To meet the increasing demand of clinical trials, study sites are increasingly using electronic systems as a strategy to support the conduct of clinical research.[2,3] The engagement in electronic systems to support research has created the need for an additional support role for the nurse to facilitate the translation of the electronic system into clinical practice. The clinical research nurse supports multiple aspects of research, which includes the implementation of electronic systems, regulatory compliance, and clinical care aspects in clinical trials.[4,5] The benefits of clinical research informatics can support safe human subject research conduct, provide transparency to clinicians regarding patient's engagement in clinical research, and increase the quality of delivered care to individuals participating in research.

Electronic systems support both the direct clinical care practice of the human research subject and the administrative regulatory oversight of clinical trial management. An understanding of the five domains of clinical research nursing scope and standards of practice include the following domains: human subjects protections, care coordination and continuity, contribution to science, study management, clinical practice, support compliance, and safety while engaging in clinical research conduct.[4,5] It is essential that the clinical research nurse maintains an up-to-date understanding and vigilance toward those users who will have access to private clinical research information to develop an understanding of where the private research information will be stored.

This article aims to provide a clinical update on regulations and compliance, clinical trial management systems (CTMS), electronic medical records (EMR), artificial intelligence (AI), and the implications for oncology nursing practice.

Regulations and Compliance

The Federal Policy for the protection of human subjects is known as the "Common Rule."[6] The Common Rule was published in the federal registrar in 1991 outlining the federal regulations for Institutional Review Board conduct, guidelines, and processes for informed consent, and assurance of compliance while conducting human subject research. In 2018, the Common Rule approved an amendment update that incorporated specific regulations to cover human subject privacy.[7,8] The revision offers a distinction between *private information* and *private identifiable information.*[6-8] The privacy of the human research participant is considered sensitive and confidential, and the use of unique study numbers are used to

* Correspondence to: Candida Barlow, MSN, CTN, RN, Bio-Optronics, 1890 South Winton Rd., Rochester, NY 14618
E-mail address: cbarlow@bio-optronics.com

https://doi.org/10.1016/j.soncn.2020.151005
0749-2081/

provide anonymity.[9] Moreover, the screening and enrollment numbers are utilized to maintain private information on submissions to sponsors and contract research organizations to ensure human research subjects remain de-identified.

Traditionally, the clinical trial record was maintained on paper source documents and then transcribed into the sponsor's electronic data system using the screening number.[10] Recent advancements in clinical research informatics now affords study sites the ability to retain source records in an electronic format.[6] The Common Rule update clarifies that electronic identifiable information for research purposes will not be made public, citing the EMR as an example.[7,8] The transition from paper-based systems to electronic platforms creates an environment of transparency and awareness combined with regulatory guidance that the clinical research nurse must learn to navigate to maintain privacy regulations.[6,11,12] The Common Rule update specifically makes reference to the EMR as a provision that can include private information, creating the need to identify who has access to the clinical research record and for what specific purposes.[6–8]

Clinical research informatics and EMR offers the ability to create separate credentialing and privileging for the end-user's access regarding the human research subject's participation in a clinical trial and their medical records. The functionality of credentialing and privileging affords multiple layers of privacy protection for the human research subject by creating transparency for the individual's safety and protocol management.[13] The EMR supports credentialing features based on the delegation of authority log, creating a partition in the medical record clearly delineating the source of truth for research clinical care from conventional clinical care.

An example of supporting the partitioning of the records could be maintained by a new medical record number or using a dedicated research financial encounter number. This allows the research record to be partitioned in a similar manner to the behavioral health medical records by enabling access based on permissions and credentialing of the individual member of the research team. The behavioral health medical record is partitioned from staff who do not have rightful access to individual patient's medical records.[11] Furthermore, the EMR leverages protocol compliance and subject safety by ensuring access 'view only' privileges to clinical teams caring for the research participant. By allowing view only access of appropriate information, the clinical teams facilitate transparency and safety notifications regarding the patient's status on the clinical trial. A comprehensive understanding and training on EMR electronic systems may empower the clinical research nurse in supporting clinical research regulations.

Common rule definition

Private information is defined as information that an individual can reasonably expect no formal recording or documentation of their behavior without the individuals consent.[6,7] Private information is classified as information provided for specific purposes of research that will not be made public.[6,7]

Good clinical practice

According to Good Clinical Practice guidelines, source data is considered as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.[14] Good Clinical Practice guidelines provide examples of source documents that may include: hospital records, clinical and office charts, laboratory notes, memoranda, participants diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, records kept at the pharmacy, laboratories, and medico-technical departments who are involved in the clinical trial.[14]

Barriers and Facilitators of the EMR

Implementing electronic source documentation into clinical research offers positive opportunities by strengthening audits, accountability, transparency, data accuracy, and efficiency in final outcomes in clinical trials.[15] Engagement in the EMR can decrease the risk of data entry errors and increase quality and compliance in clinical trials.[12] The EMR contains the medical history of the research participant and past historical information of family members. The Common Rule underscores that the research participant's personal private information must be respected and maintained private, creating a challenges for the clinical research nurse.[6,7] The challenge to the clinical research nurse using the EMR as source documents for the study-related progress and clinical notes is that many individuals have access to the EMR. Health care professionals, insurance companies, legal summons from court records can all have access to the EMR.[16] The clinical research nurse must recognize that the research clinical records must be partitioned from the main part of the EMR records for all study subjects, likened to the access privileges of Behavioral Health Record.

In the process of transitioning the clinical research records into an electronic format it should include all key stakeholders, which might include: the clinical research teams, legal, risk management, and compliance professional teams. Creating an internal working group will help to determine the new electronic processes to ensure protection of the research participants' private identifiable health information. Determinations regarding the level of access and information that is viewable can be identified by key stakeholders during the deployment of new electronic systems.[11] Clinical research sites may employ a clinical research nurse who holds a unique role overseeing data in the EMR and Electronic Source environment. The clinical research nurse is a key support member, bridging the two clinical worlds with separate regulations and laws.[17]

Source Data and Source Documents

The source documents are key in the conduct of the clinical trial. Source documents are defined as 'original documents, data and records' and, in contrast, source data is considered as actual data that can be found in source documents and certified copies, where the actual data point related to the data collection was entered.[10] Integrating source documents into the electronic platform creates a new landscape for the definition of source documents, now referred to as eSource Documents. A benefit to transitioning to eSource Documents is directly related to Attributable, Legible, Contemporaneous, Original, Accurate and Complete (ALCOA) documentation standards.[18] The standard requirement for reporting on ALCOA can now be managed through electronic systems by ensuring ALCOA is met, per the ICH E6 4.9 records and reports standard.[18]

Electronic systems create a complex landscape presenting an integrated source document. It is critical for the clinical research nurse to understand where the 'source' of truth is found within each electronic system.[10] For example, the CTMS and EMR can be integrated, pushing and pulling private identifiable information. The process of data mapping and identifying the source of truth data entry points should be documented in the sites standard operating procedures.

EMR Regulations and Guidelines

The US Food and Drug Administration (FDA) guidance document outlines EMR systems, and states that if they meet the basic tenants of the Office of the National Coordinator for health Information Technology (ONC) Health IT Certification Program then they are 45 CRF §170 compliant.[19] ONC certification validates the EMR records usage for source data and fulfills the requirement to enable electronic signature and audit trail requirements.[8,11] Maintaining copies of the ONC certificate in the regulatory binders for the clinical research site supports compliance and best practices.[19,20]

eConsent

The informed consent process in clinical trial requires sound ethical conduct in keeping with Good Clinical Practice guidelines.[4,5] The scope and standards of the Clinical Research Nurse by the American Nurses Association and International Association of Clinical Research Nurses outlines the consent process by engaging all aspects of the nurse's education, training, and skill integrated with Good Clinical Practice guidelines.[4,5] The use of the electronic informed consent offers electronic web-based interactive engagement with the research participant during the process of the informed consent.[4,5] The eConsent provides a real-time tracking documenting of the informed consent process and is approved by the FDA regulations for consent documentation.[21] The eConsent supports pre-recorded videos, hyperlinks to definitions, and interactive images related to the clinical trial to support patients with different levels of health literacy.[22] Given the increasing complexity of cancer clinical trials, the clinical research nurse has an integral role in protecting the rights of the research participants by ensuring informed consent.[23] The trial-specific educational materials embedded in the eConsent can support an increased level of understanding and may empower the individual considering participation in a clinical trial.

eConsent Regulations

Electronic informed consent is set forth by 21 CFR parts 11, 50, and 56 and 45 CFR part 46 indicate that the use of electronic systems and processes that use multiple electronic media, including text, graphics, audio, video, podcast, passive and interactive Web sites, biological recognition devices, and card readers to convey information related to the study to obtain and document informed consent meet the definition of eConsent.[12,21,24,25] The main tenants of research participant protection relating to the informed consent remain the same as utilizing traditional paper document consent. The use of an eConsent is not less restrictive or does not decrease accountability or responsibility.[12,25] A specific statement in the FDA guidance document for eConsent states that an investigator cannot delegate authority to obtain informed consent to the electronic system. The act of informed consent, whether it be paper or electronic based, still requires a qualified, trained, and educated member of the research team.[12,25] eConsent can be obtained remotely, and there must be a clear process whereby the study personnel can personally verify the individual's identification, review the eConsent, and answer questions about the study, provide an opportunity to answer questions, and witness the signing of the eConsent.[12,21,24, 25] Examples of methods that can be used remotely to verify the study participants include: the use of personal questions for access to the system, biometric methods, and visual methods.[25]

Clinical Trial Management

A Clinical Trial Management System (CTMS) offers site efficiencies in compliance, time management, increased financial tracking, and reconciliation, as well as tracking and scheduling of study subject visits, and regulatory compliance oversight.[26] The CTMS also offers a repository for study-specific source of truth, participant and study data entry, and compliance controls in the system. The CTMS is a source of truth for research information that can push updates to the EMR system should the integration support bi-directional data feeds (which means pushing data from one system [EMR] into another system [CTMS]). It is important to note that the source of truth for the research tracking and monitoring originate in the CTMS and the clinical care for research participant originates in the clinical documentation for source of truth. Study participant's status such as enrollment, randomization, and long-term follow-up, can push and pull data (bi-directional feeds between systems) validating the "source of truth."

Electronic systems can allow for the full integration between the EMR and CTMS system, which is a tremendous benefit and automates validation of research subjects and decreases the potential for fraudulent or erroneous enrollment.[27] Noteworthy, not all electronic systems are equal in capabilities. The CTMS can support time management and efficiencies for the clinical research nurse by tracking participants, study visits, and timelines procedures related to the study protocol.[28]

EMR and CTMS Interoperability

Technologic integration of the EMR and CTMS affords optimal clinical management. Clinical patient care systems within the EMR are integrated into the CTMS system that can allow real-time communication platform for both study and clinical teams.[29] Administrators can track adverse events, deviation rates, trial outcomes, and trends across multidisciplinary trial spanning across all phases of trial conduct. CTMS and EMR integration also provides robust research support services utilizing large centralized data sets. The integration of these systems enables research opportunities that range from study search capabilities to identify new study opportunities to networking in large research studies across multiple systems.[29]

AI

Predictive analytics in clinical research are supported using AI. AI can look at algorithms and identify potential clinical solutions based on analyzing data sets linking, for example, biomarkers, research results, EMR records, scoring systems, prognosis, readmission, and morbidity and mortality rates. Currently, two areas of clinical research practice that have engaged AI to help solve complex problems within the clinical research industry.[30] The first use of AI is implemented using radiology and complex medical imaging. Radiology and Enterprise Medical Imaging Extensions (REMIX) support the use of 'big imaging data' throughout large multi-disciplinary oncology trials.[30] Advancement in technology using AI can detect the type of cancer compared with the trained naked eye. For example, breast cancer CT scanning images can be analyzed through electronic AI systems and has the power to detect microscopic mases much earlier than a trained radiologist.[30] The clinical trial industry is currently embarking upon a new landscape of regulatory compliance and governance regarding use of AI results for clinical trials.

Serious Adverse Event and Adverse Event Oversight

Safety functionality can be incorporated within the CTMS and EMR systems to monitor serious adverse events and adverse events. The Health Information Technology system offers the information technology teams and the research team the ability to build safety reporting embedded in the registration systems.[31] The safety reporting feature increases the ability to respond and record a serious adverse event (SAE) or capture an adverse event (AE) when a research participant is admitted for hospital or regular care within a health system, which in turn increases adherence and regulatory compliance requirements.

Recruitment and Retention Considerations Using Electronic Platforms

The functionality of the CTMS and EMR systems can screen potential study participants for clinical trial recruitment and enrollment. There are a few key pieces of information to consider when utilizing either the CTMS system or the EMR system to screen and recruit potential research subjects. The potential human research participant must first have provided informed consent to be pre-screened. The ability to access either system does not warrant the ability to freely open charts and screen individuals' personal private medical records. There are several methods to obtaining consent for pre-screening

during a clinical trial; the first is through preparatory research practices. Research preparatory practices are covered under the HIPPA privacy rule and sections 45CFR164.[11] Another area that clinical research teams can disclose preparatory practices for research can be within the institution's privacy statements that are disclosed to all patients entering the facility for treatment.

The use of electronic systems can support efficiencies in prescreening and screening logs.[11] Entering the data into the CTMS system offers the clinical research nurse the ability to export de-identified records to study sponsors for reimbursement and recruitment efforts, omitting paper screening logs. When the EMR and the CTMS are integrated together, this may release the clinical research nurse time to focus efforts on clinical trial recruitment efforts. The EMR system can create rules and alerts to screen for eligible research subjects based on laboratory results, diagnostic reports, and other various data points.

Screening and Recruitment Impact of AI

The second largest impact of AI to the clinical research industry is the use of clinical research informatics for screening and recruitment of clinical research participants. With e-consent, selection and recruitment may no longer be a cause of a delay in accrual. Additionally, electronic systems can create data queries that search for specific inclusion and exclusion criteria or identify types of patients for screening. For example, an oncology trial may include inclusion and exclusion criteria to identify an ECOG score of less than 2 with ductal carcinoma in situ. Analytics can then capture the inclusion and exclusion criteria, increasing study subject identification. Furthermore, there are now electronic systems that are cloud-based that can search the EMR record based on specific inclusion and exclusion criteria to identify potential study subjects, making research recruitment and feasibility more efficient. Utilization of information technology decreases the study team's work effort and the overall cost and time to conduct a clinical trial.

AI can send out automated alerts for regulatory, patient, and compliance support. The CTMS and EMR, using an integrated system approach, can alert the research team when a study subject is admitted or enters the emergency room. The clinical research nurse has a myriad of increased opportunities that are support by utilizing clinical research informatics systems. Utilization of clinical trial informatics systems increases study participants' safety and compliance while providing tools for the clinical research nurse to monitor and manage clinical trial protocols. This can equate to a decrease in workload and an increase in efficiency by automating clinical trial management operations.

Implications for Oncology Nurses

The oncology research nurse must understand the new privacy determinations outlined in the new Common Rule updates from 2018 while engaging in clinical research conduct. The privacy updates apply to electronic systems and charting practices for the clinical research nurse. A robust understanding of the regulations regarding clinical research conduct and the use of electronic informed consent practices will facilitate the oncology research nurse in delivering high-quality and safe care to the research participant.

Conclusion

Clinical research informatics is an exciting and emerging field empowering clinical research nurses to improve clinical research care and monitoring for human research participants. As the clinical research informatics industry matures, the clinical research nurse will need to keep up-to-date and continue to practice within complex electronic regulatory landscapes. The clinical research nurse should be committed to continual professional development with regard to electronics systems to support optimum clinical care management and delivery of the human research participant.

References

1. Getz K, Campo R. Trends in clinical trial design complexity. *Nat Rev Drug Discov*. 2017;16:307.
2. Caballero Munoz E. Hullin Lucay Cossio CM. Engaging clinicians in health informatics projects. *Stud Health Technol Inform*. 2010;151:195–206.
3. Vulcano D, Barlow C, Scully N, Soto-Azghani C, Keyes A, Ziemba S. Maximize your EHR for clinical trials operations. *Clinical Researcher*. 2016. Available at: https://acrpnet.org/2016/06/01/maximize-ehr-systems-clinical-trials-operations/.
4. American Nurses Association and International Association for Clinical Research Nursing. *Clinical research nursing: scope and standards of practice*. Silver Spring, MD: American Nurses Association & IACRN; 2016.
5. American Nurses Association. *Code of ethics for nurses with interpretive statements*. Silver Springs, MD: Nursesbooks.org; 2010.
6. US Department of Health and Human Services, Office of Human Research Protections. Revised Common Rule. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1. (Accessed 20 December 2019).
7. Electronic Code of Federal Regulations. Health Information Technology Standards 45 CFR§ 46.102. 2018. Available at: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML. (Accessed 20 December 2019).
8. US Department of Health and Human Services, Office of Human Research Protections. 45 CFR 46: 2018Requirements. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html. (Accessed 20 December 2019).
9. US Department of Health and Human Services. HIPPA privacy rule information for researchers. Available at: https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html. (Accessed 20 December 2019).
10. US Food and Drug Administration. Electronics source data in clinical investigations: guidance for industry. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-source-data-clinical-investigations. (Accessed 20 December 2019).
11. US Department of Health and Human Services, National Institute of Health. Protecting personal health information in research: understanding the HIPAA privacy rule. Available at: https://privacyruleandresearch.nih.gov/pr_02.asp. (Accessed 20 December 2019).
12. US Food and Drug Administration. Use of electronic health record data in clinical investigations: Guidance for industry. Available at: https://www.fda.gov/media/97567/download. (Accessed 20 December 2019).
13. De Carvalho MA, Bandiera-Paiva P. Evaluating ISO 14441 privacy requirements on role-based access control (RBAC) restrict mode via Colored Petri Nets (CPN) modeling. International Carnahan Conference on Security Technology (ICCST), Security Technology (ICCST), 2017 International Carnahan Conference on. October 2017:1-8. Available at: https://ieeexplore.ieee.org/document/8167833.
14. ICH. Integrated addendum to ICH. E6(R1): Guideline for good clinical practice E6 (R2). 2016. Retrieved from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf. (Accessed 20 December 2019).
15. Kellar E, Bornstein S, Caban A, et al. Optimizing the use of electronic data sources in clinical trials: the technology landscape. *Ther Innov Regul Sci*. 2017;51:551–567.
16. Colosi HA, Costache C, Colosi IA. Informational privacy, confidentiality and data security in research involving human subjects. *Applied Medical Informatics*. 2019;41(1).
17. American Nurses Association. *Nursing informatics: scope and standards of practice*. Silver Spring, MD: American Nurses Association; 2008.
18. Good Clinical Practice Network. 4.9 Records and reports. 2018. Available at: https://ichgcp.net/49-records-and-reports/. (Accessed 20 December 2019).
19. HealthIT.gov. Implementation specifications: certification criteria & certification programs. Available at: https://www.healthit.gov/topic/certification-ehrs/certification-health-it. (Accessed December 20, 2019).
20. US Food and Drug Administration. Guidance for industry computerized systems used in clinical trials. Available at: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/guidance-industry-computerized-systems-used-clinical-trials. (Accessed 20 December 2019).
21. US Department of Health and Human Services. Use of electronic informed consent: question and answers guidance for institutional review boards, investigators, and sponsors. Available at: https://www.fda.gov/media/116850/download. (Accessed 20 December 2019).
22. Regan EM. Clinical trials informed consent: an educational intervention to improve nurses' knowledge and communication skills. *J Clin Oncol Nurs*. 2018;22:E152–E158.
23. Ness EA, Royce C. Clinical trials and the role of the oncology clinical trials nurse. *Nurs Clin North Am*. 2017;52:133–148.
24. US Food and Drug Administration. Part 11, Electronic records; electronic signatures. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application. (Accessed 20 December 2019).
25. US Food and Drug Administration. Part 50. Subpart B. Elements of informed consent. 21CFR § 50.25. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25. (Accessed 20 December 2019).
26. Park YR, Yoon YJ, Koo H, et al. Utilization of a clinical trial management system for the whole clinical trial process as an integrated database: system development. *J Med Internet Res*. 2018;20:e103.

27. Beck C, Dumay J, Frost G. In pursuit of a "single source of truth": from threatened legitimacy to integrated reporting. *J Business Ethics*. 2017;141:191–205.
28. Bio-Optronics. Taking control of project management by using a CTMS application. Available at: https://bio-optronics.com/ctms/blog/project-management-by-using-a-ctms-application-2/. (Accessed 20 December 2019).
29. PR Newswire. Adventist Health System, Bio-Optronics partner on CTMS deployment to foster clinical research excellence. PR Newswire US. Available at: https://bio-optronics.com/press/adventist-health-system-bio-optronics-partner-ctms-deployment-foster-clinical-research-excellence/Published April 27, 2017. (Accessed 20 December 2019).
30. Sadoughi F, Kazemy Z, Hamedan F, Owji L, Rahmanikatigari M, Azadboni TT. *Artificial intelligence methods for the diagnosis of breast cancer by image processing: a review*. 10. Breast Cancer (Dove Med Press); 2015:219–230.
31. Bellows BK, Kuan-Ling K, Biltaji E, et al. Real-world evidence in pain research: a review of data sources. *J Pain Palliat Care Pharmacother*. 2014;28:294–304.