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Cover Page Footnote

Correspondence To: Julio A. Ramirez, MD Work Address: Division of Infectious Diseases, University of Louisville Work Email: j.ramirez@louisville.edu Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

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Research Support Infrastructure: Implementing a Clinical Research Coordinating Center

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Abstract

Insufficient infrastructure is one of the challenges facing investigators in the field of clinical research. At the University of Louisville (UofL) Division of Infectious Diseases, we developed a multidisciplinary coordinating center with the aim to support investigators in all aspects of the clinical research process. The objective of this article is to describe the composition and the role of the different units of the UofL Clinical Research Coordinating Center. The different components of the Center can serve as a template for institutions interested in developing a clinical research support infrastructure.

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Introduction

Performing clinical research is a complex operation that requires the collaboration of a multidisciplinary team. For clinical investigators to be successful they need to have a clinical research support infrastructure that combines the wide array of expertise of different team members. With the goal to support clinical research in the Department of Medicine, we developed a Clinical Research Coordinating Center (CRCC) at the University of Louisville (UofL) Division of Infectious Diseases.

In this paper, first we will review the most common clinical research studies and perform an overview of the clinical research process. Second, we will describe the role of the different units of the Clinical Research Coordinating Center developed at the UofL Division of Infectious Diseases. The different components of the Center can serve as a template for institutions interested in developing a clinical research support infrastructure.

Clinical Research Studies

Biomedical research is broadly structured as basic research and clinical research. In clinical research, medical knowledge is advanced by performing studies that involve a direct interaction with human subjects or an indirect interaction through the collection and analysis of human samples (e.g. blood, tissues) [1]. If during the interaction with a human subject the investigator applies any form of intervention, the clinical study is classified as an interventional study. Interventions may include drugs, procedures, vaccines, use of medical devices, or noninvasive methodologies such as interviews, surveys, or educational activities. In a clinical trial, human subjects are

prospectively assigned to receive an intervention according to a defined protocol evaluating the effect of such intervention in a particular outcome. Clinical trials are a critical aspect of the clinical research enterprise, but clinical trials constitute only a small fraction of clinical research activities. If the investigator does not apply any intervention and subjects will be only observed, the clinical study is classified as an observational study.

In observational studies, participants may receive interventions such as diagnostic tests or treatments, but the investigator does not assign the participant to a particular intervention. In an observational study, interventions are given as part of standard medical practice. Some of the most common interventional and observational clinical research studies are depicted in **Figure 1**.

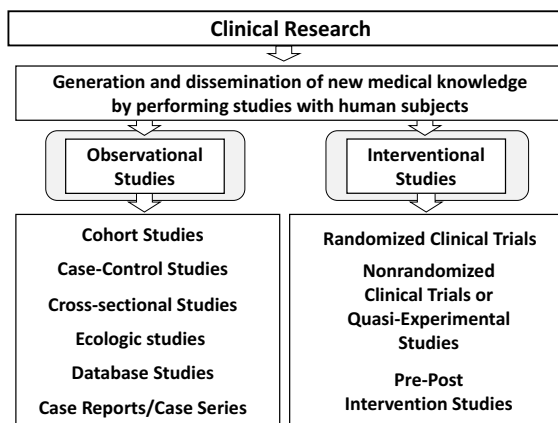


Figure 1. Common study designs in clinical research

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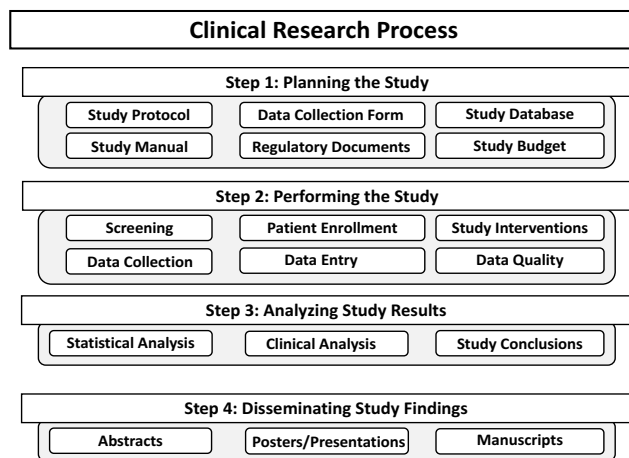


Figure 2. Steps in the Process of Clinical Research

Clinical Research Process

The process to perform clinical research studies can be summarized in four steps (Figure 2). During the first step, planning the study, the research team will need to develop the study protocol, data collection form, study database, study manual, regulatory documents, and study budget. During the second step, performing the study, the research team will need to perform screening, patient enrollment, interventions and study follow-up activities, data collection, data entry, and data quality. During the third step, analyzing the study results, the research team will need to perform statistical analysis, clinical analysis, and develop study conclusions. During the fourth step, disseminating study findings, the research team will write abstracts, posters, and manuscripts for publication in peer-review journals. Findings may also be shared through formal and informal presentations. With these steps in mind, we developed a Clinical Research Coordinating Center to guide and support investigators during the clinical research process.

Clinical Research Coordinating Center

The CRCC is composed of different units, with each unit in charge of supporting a particular area of clinical research. The current units and personnel of the CRCC are depicted in Figure 3. The primary roles for each of the units are summarized below.

Strategic Planning & Administration Unit: This unit serves as the leadership function for the CRCC and, as such, sets the primary goals for the other units of the CRCC, provides oversight of the administrative duties of all units, and ensures that the necessary resources are available. Members of this unit serve as the primary liaisons between clinical investigators and members of other units within the CRCC.

Clinical Operations Unit: The interactions with study participants and the collection of data are at the heart of clinical research. To conduct clinical studies efficiently and effectively we need to maintain a quality group of clinical research associates/study coordinators and ensure that best clinical practices are followed. The clinical operations unit develops standard operating procedures (SOPs) for clinical operations, manual of operations, and data collection forms relevant to each individual clinical study. The unit performs training and competency validation of study teams in all aspects of performing the study.

Regulatory and Financial Unit: To protect the safety and welfare of study participants, clinical studies are highly regulated. Another important aspect of clinical research involves financial compliance. We decided to combine the regulatory and financial management into one unit. The primary activities of this unit include development of study consent forms and other regulatory documents; serving as liaison with the Institutional Review Board (IRB) and research offices at the different sites; preparing all documents required IRB submissions; reporting protocol deviations and severe adverse events to the IRB; verification of IRB approvals including all study documents and at all clinical sites, verification of amendments at all clinical sites to ensure appropriate protocol, consents and other documents are being used; and assuring that all relevant IRB correspondence (continuing review and amendments) and study status changes are communicated in real-time to all sites. The unit is also in charge of credentialing all research staff at participating facilities and monitoring of study payment milestones.

Database Management Unit: For every clinical study, a versatile study database will need to be designed. Members of this unit have expertise with the use of REDCap® (Research Electronic Data Capture) [2]. REDCap® provides investigators with a software tool that facilitates the development of a specific research database according to the particular research project. REDCap® is now a collaborative international consortium and includes over 300 institutions across the world.

The primary activities of this unit include development of study databases utilizing REDCap® software. In conjunction with the Clinical Operation Unit and the Statistical Analysis Unit, this unit is also responsible for development of the data dictionary to ensure an appropriate mapping from the case report form to the electronic database, and consistency for statistical analysis. The unit is also in charge of providing data security for the clinical data during data collection, transmission, and storage.

Research Informatics Unit: Members of this unit develop technology and tools that facilitate clinical research activities. This can include the design of websites for monitoring the study, maintaining clinical software infrastructure, and designing IT policies that facilitate study success. The unit also helps with the management of information from clinical studies and large databases.

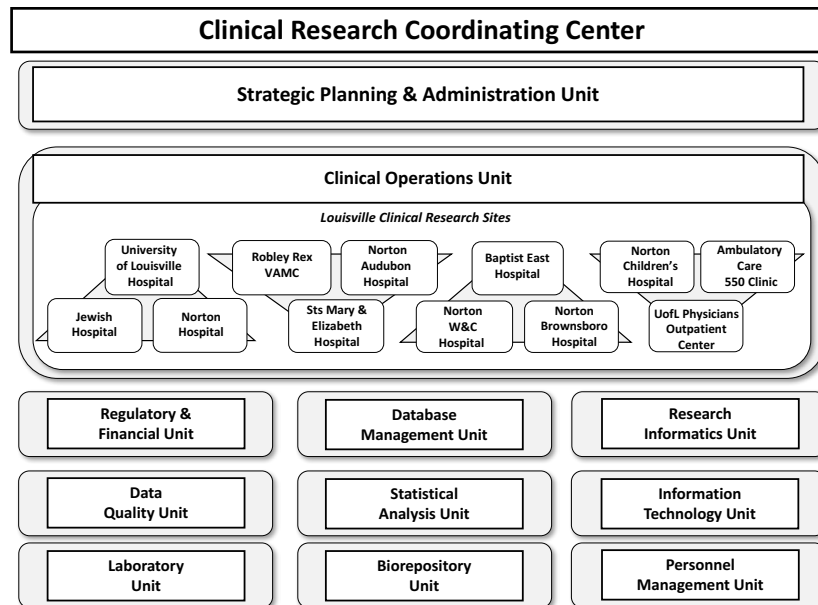


Figure 3. Structure of the Clinical Research Coordinating Center

Data Quality Unit: Data quality and integrity is a critical component of clinical research. By minimizing missing data and the number of errors, only high-quality data will be available for analysis. Members of this unit assure the identification of eligible patients based on study criteria in both the screening and enrollment processes. The unit ensures data validity through the generation and addressment of data quality queries and data quality rules in REDCap®.

The data quality management procedures are depicted in **Figure 4**. Briefly, a study coordinator/research associate collects data from the patient's medical record onto a paper-based case report form (**Figure 4, Point A**). A separate study coordinator/research associate transfers the data on the paper case report form to the electronic case report form (**Figure 4, Point B**). Next, a staff member from the CRCC examines the submitted electronic case report form for submission into the unverified study database (**Figure 4, Point C**). Finally, members of the CRCC perform analysis of the data searching for common errors (**Figure 4, Point D**). Data quality evaluations are performed for points B, C, and D in **Figure 4**. Discrepancies at any level of data quality generate queries that will be corrected by the study coordinator who collected the data from the patient's medical record (**Figure 4, Point A**). As part of our local data quality process, we expect study coordinators to resolve all queries within seven days. After discrepancies are resolved, a final verified study database is compiled.

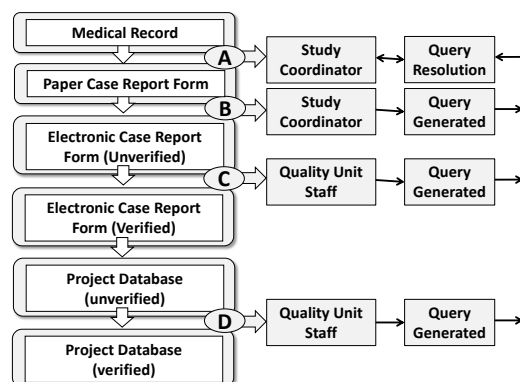


Figure 4. Data Quality Process

Statistical Analysis Unit: Collaboration with statisticians is important at every stage of a clinical study, from planning the study, ensuring data quality, data analysis, and interpretation of study results. The statisticians in the unit perform real-time descriptive and inferential statistical analysis and visualization of study data performed using R: The R Project for Statistical Computing, ArcGIS, and SaTScan software. Real-time data visualization with graphical outputs such as boxplots, histograms, and maps are developed. This team is also responsible for examination of aggregate data to identify potential site variations. These results can then be shared with other units that can identify reasons for such variation then develop and implement a corrective process.

Information Technology Unit: Exchange of electronic data using computers and other physical devices, is an important activity of the clinical research operation. To secure the proper maintenance of computers, software, and networks among members of the CRCC, we created an information technology unit. Members of this unit determine then secure an optimal functioning of employee technology, detailed inventory of hardware and software, and the addressment of technological issues as needed by utilization of an IT ticket system.

Laboratory Unit: A reference laboratory is an integral part of the coordinating center. This laboratory supports clinical studies by perform special tests according to protocol requirements. In addition, the laboratory unit maintains an environmental scan that seeks to identify new tests or testing methods that may impact existing and planned studies.

Biorepository Unit: As samples of clinical material are obtained as part of clinical studies, the clinical investigator will need to create and maintain a biorepository. Members of this unit develop and implement procedures for study supplies, specimen processing and maintenance, and analysis. The unit tracks and ships specimens, including documentation of receipts, and stores study specimens and their locations within REDCap®.

Personnel Management Unit: To better serve the needs of our expanding number of clinical research members it became

necessary to develop a personnel management unit. Members of this unit address the human resources elements of the CRCC and ensure compliance with local, state, and federal policies and procedures, hiring of new employees, processing payroll, management of employee leave requests, schedules and calendar management.

Conclusions

Clinicians in academic centers are frequently involved in clinical research. The interaction with patients will generate research questions expanding from disease pathogenesis, diagnostic techniques, management strategies, to new therapeutic approaches. The process necessary to move from a research question to a publication is a complex enterprise. In this paper, we described the implementation of a Clinical Research Coordinating Center as a way to help clinicians involved in clinical research. Institutions that want to foster clinical research will need to implement a comprehensive clinical research support infrastructure. The example of the UofL Clinical Research Coordinating Center may serve as a scalable model that can be used by other researchers and institutions as they seek to implement new or improve existing clinical research capabilities.

Clinical Research Coordinating Center Team:

Senen Peña, Andrea Reyes, Sarah Van Heiden, Eman Abbas (strategic planning & administration unit), Eddy Reyes, Kuldeep Ghosh, Bilal Abaid, Vidyulata Salunkhe, Yasmany Garcia (clinical operation unit), Kendra Thompson (regulatory & financial unit), Kimberley Buckner (database management unit), Stephen Furmanek (statistical analysis unit), Mohammad Tahboub (data quality unit), Chris Dixon (information technology unit), Subathra Marimuthu (biorepository unit), and Emily Just (personnel management unit).

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