Study Coordination and its Key Role in Clinical Research

Coordenação de Estudos e o seu Papel Fundamental na Investigação Clínica

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Abstract

We have been seeing a growing body of work showing the benefits of having health institutions investing in clinical research – health outcomes appear to be better, following of guidelines, and consequent patient care are also improved. The existence of a Clinical Research Support Unit seems essential, ensuring patient safety and quality of data, by supporting with time-consuming and expertise-requiring tasks. The inclusion of a Clinical Research Coordinator is thought to carry many advantages, as a considerable amount of responsibilities will be delegated to this professional.

This review adds onto the current literature on the role a Clinical Research Support Unit and a Clinical Research Coordinator have on clinical research, as well as the benefits they bring.

A strong unit gives rise to efficient, quality research, which in turn leads to improved, optimally delivered healthcare services, improved outcomes, enhanced infrastructures, job creation, and cost savings. The presence of a Clinical Research Support Unit with a professional Clinical Research Coordinator team not only facilitates industry-sponsored research but also enables the development of investigator-initiated studies. Further studies on the medical and socio-economic effects of high-quality clinical research activity in Portugal are both justified and necessary.

Keywords: Biomedical Research; Clinical Protocols; Clinical Trials; Research Personnel

Resumo

Há cada vez mais literatura sobre o benefício das Instituições de Saúde em investirem em Investigação Clínica (IC) – os *outcomes* clínicos parecem ser melhores, a integração das diretrizes mais eficaz e consequentemente, vemos uma melhoria na prestação de cuidados de saúde ao doente. A existência de Unidades de Apoio à Investigação Clínica (UAIC) torna-se essencial, dando suporte nas tarefas que exigem tempo e expertise e garantindo a segurança do doente e a qualidade dos dados. A integração de um Coordenador de Investigação Clínica (CIC) numa equipa de investigação parece trazer inúmeras vantagens, pois o mesmo poderá ficar responsável por uma boa parte das atividades de IC.

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Esta revisão narrativa complementa a literatura atual sobre o papel que uma UAIC e um CIC têm na Investigação Clínica, bem como os benefícios que estes trazem.

Uma UAIC sólida dá origem a investigação eficiente e de qualidade, o que, por sua vez, leva à melhoria e otimização da prestação de cuidados de saúde, dos *outcomes* e das infraestruturas, bem como à criação de postos de trabalho e redução de custos.

A presença de uma UAIC em conjunto com uma equipa especializada de CICs não só facilita a condução de estudos promovidos pela Indústria, mas também permite o desenvolvimento de Estudos da Iniciativa do Investigador.

Torna-se evidente a necessidade de serem desenvolvidos mais estudos em Portugal sobre o impacto clínico e socioeconómico da Investigação Clínica de excelência.

Palavras-Chave: Ensaios Clínicos; Equipa de Investigação; Investigação Biomédica; Protocolos Clínicos

Introduction

Clinical research is a key tool for advancing medical knowledge, playing an important role in discovering new treatments and making sure that the existing treatments are used in the best way possible in clinical practice. On a similar note, patient care also seems to be improved in a research-active institution,[1] with possible better outcomes[1–4] due to following protocols,[5] improved adherence to guidelines and use of evidence by practitioners.[6,7] Ultimately, high-quality clinical research helps the national health systems improve future healthcare.

Despite all benefits and interests associated, clinical research in Portugal and similar high-income countries still appears to be vulnerable to several factors. Lack of funding, specialized support, available time, and appropriate training seem to be important barriers.[8–14] Clinical research lacks sufficient clinical research-specific training programs nationwide, particularly the incorporation of formal, didactic coursework in areas such as protocol design, statistics, research ethics, and regulatory demands. Evidence of this is a significant number of Portuguese physicians, health care professionals and medical students, including those who participate in research, not being aware of the Good Clinical Practice (GCP) Guidelines and subsequently not being GCP certified.

Benefits of physicians participating in clinical research include professional growth, advantages for both clinical practice – where vanguard treatment and interventions can be delivered to the patient – and clinical research, and opportunities to contact with other professionals in their scientific area.[15–17] Although assimilation of the two roles is not an easy task,[16,18] physicians need better balance between clinical activity and clinical research, so they can both participate in industry-sponsored and develop investigator-initiated research.

Regarding lack of time and competing priorities, clinical research is not sufficiently promoted on the daily clinical practice of physicians, young physicians in training and other health care professionals.[19] To achieve high-quality clinical research, the research team must have enough availability to be able to comply with study protocol-specific tasks, frequently with strict deadlines, and GCP. A Clinical Research Coordinator (CRC) and adequate planning are ways to manage this drawback.[17] Operational and organizational structures are needed to combat this gap,[19–21] and a strong study site will make the physician's research activity possible, by helping with many time-consuming ordeals.

The Role of a Clinical Research Support Unit in a Research Center

The Clinical Research Support Units (CRSUs), have been implemented in Portuguese research sites in the last few years, normally directly associated with universities or other scientific and research institutes, such as non-profit organizations.

A CRSU is a centralized group of individuals with specific and specialized roles that provides essential support for both investigator-initiated and industry-sponsored clinical trials.[22] The main mission of a CRSU is to assist Investigators in the conduct of clinical studies, by providing several services including regulatory support, study conduct and management support,[21,22] and ultimately increasing research credibility.[23] Another principal objective of the majority of CRSUs is to educate medical students, graduate students and health care professionals in agreement to the highest professional standards; to prepare aspiring clinicians to practice patient-centered medicine as well as to assume leadership roles in medical practice, education, and research. CRSUs promote the development of a comprehensive, translational and multi-disciplinary training environment for graduate students intended to prepare young researchers to become future leaders in the different areas of research.

CRSUs are also designed to serve as a platform for investigators from a broad range of disciplines. This allows collaboration between different departments within the study site, in the greater academia community in Portugal and internationally. The principal focus of each CRSU is to establish a nationally and internationally recognized study site of excellence in clinical research.

A research team should be a multidisciplinary group of people working together in a systematic and scientific manner, committed to applying the principles of GCP in the conduct of clinical research in order to ensure the safety and well-being of human subjects. Normally a research team is composed of the Principal Investigator (PI) and Co-investigators, a Clinical Research Coordinator (CRC), study nurses, other healthcare professionals and a pharmacist.

The PI is the individual who actually conducts the clinical study or research study, i.e., the leader of the research team at the study site. The PI should be an appropriately qualified person in the relevant field of health care (MD, PhD), trained and experienced in clinical research, and familiar with the study requirements, protocol, investigational medicinal product (IMP) and overall procedures.

The Role of a Clinical Research Coordinator in a Research Team

The CRC, also called Study Coordinator (SC), is a specialized research professional, responsible for the conduct of study protocol at the study site level. Adequate training in the technical requirements of clinical research, GCP, and common Standard Operating Procedures (SOPs) is of utmost necessity to ensure high-quality work, and an experienced professional is preferred. Working with and under the direction of the clinical PI, an interdependent relationship is essential.[24] While the PI is primarily responsible for the overall design, conduct, and management of the clinical research, the CRC supports, facilitates and coordinates the daily clinical study activities, playing a critical role in the conduct of the study.[17,25,26] The CRC should be organized, meticulous about data, with information technology skills, capable to solve problems, deadline-oriented, communicative and a team worker, as well as familiar with both clinical matters and regulations.[17]

The CRC works closely with the PI, co-investigators, study nurses, pharmacists and other healthcare professionals to perform protocol management for each stage of the clinical study (Fig. 1). For sponsored studies, the CRC acts as a liaison between the PI and sponsor and is responsible for coordinating visits with the sponsor/Clinical Research Organization (CRO) and other relevant members of the site, as well as for arranging opportune meetings between PI and study representatives.

The CRC has several responsibilities - the primary being extracting data from the medical records and other necessary sources - and is involved in several steps of the clinical study process[27] including protocol review, forms' design, eligibility confirmation, participant scheduling and registration, and responding to requests for missing data and other queries. The CRC is also responsible for conducting clinical research using GCP under the responsibility of the PI, and must assure that all studies are conducted ethically, as defined by the Declaration of Helsinki[28] and by the International Conference on Harmonization (ICH) Guidelines.

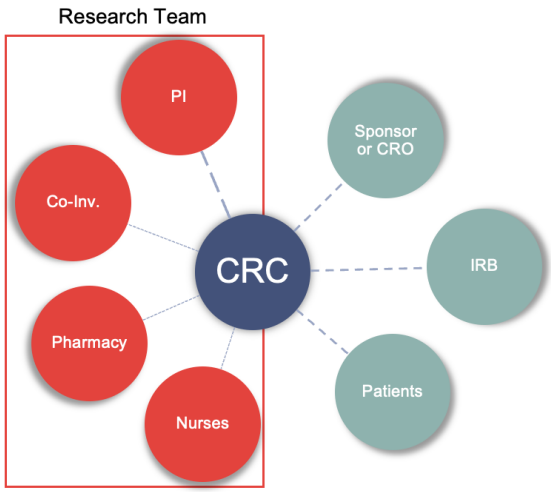

Figure 1. The role of the CRC as a contact point.
Co-Inv = Co-Investigators. PI = Principal Investigator. CRO = Contract Research Organization. IRB = Institutional Review Board.

Since the early beginning at the feasibility agreement until the close-out of the study, specific CRC responsibilities include (Fig. 2):

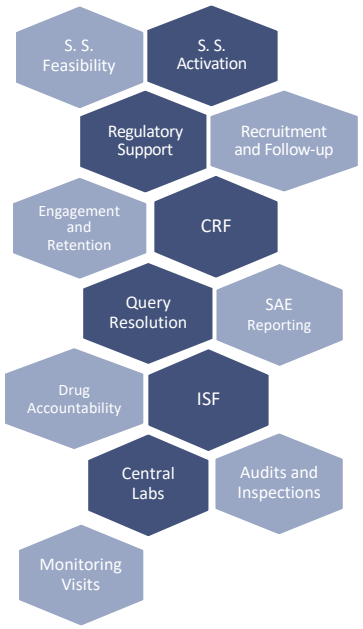

Figure 2. CRC Responsibilites.
S.S. = Study Site. CRF = Case Report Form. SAE = Serious Adverse Event. ISF = Investigator Site File.

Study Site Feasibility

The CRC supports, facilitates and coordinates all feasibility and qualification processes, including the evaluation of a potential site target, the possibility of competitiveness with other ongoing studies and adequate human resources. Additionally, the CRC performs all communication between the sponsor, PI and institution, which optimizes all the processes and turns them drastically less time-consuming.

Study Site Activation

The CRC organizes all procedures in order to activate the study, from preparing all necessary center specific documentation together with the sponsor/Contract Research Organization (CRO) - which must be presented to the local Ethics Committee and Competent Authorities (for interventional studies)-, to organizing a meeting with the study team in order to discuss study protocol as well as the division of the study procedures and responsibilities. The CRC also ensures that the site does not initiate the study before all regulatory and competent authorities' approvals, taking into account all country specifications.

Regulatory Support

The CRC assists the PI with correspondence with the regulatory authorities, such as the Institutional Review Board (IRB), and/or the sponsor to ensure that all requirements are met. The CRC may be responsible for completing several documents/forms such as new submissions, continuing review reports, amendments and protocol violations/deviations, investigational new drug safety reports, and serious adverse events (SAEs) reports.[24,29]

Additionally, the CRC should possess a complete understanding of the following protocol elements, essential to running a study and ensuring protocol compliance:

Subject Recruitment and Follow-up

Not often in Portugal, but quite frequently worldwide, the CRC plays a major role in the enrollment of study participants. The CRC should verify the potential participant's eligibility by reviewing the criteria outlined in the approved protocol and confirm that all required tests and screening have been performed. Regarding the patient informed consent form, the CRC should confirm if the most current version is being used and guarantee it is correctly dated and signed by both patient and investigator.

Participant Engagement and Retention

The CRC is responsible for most communications with the participant, and therefore quickly becomes a highly important figure, perceived as supportive and worthy of trust. The maintenance of this relationship is essential to ensure participant retention, as sometimes the study and its procedures might seem overwhelming for non-technical individuals. Participants should sense they can depend on the CRC to answer questions or worries about the study, and the CRC should be as accessible as possible, as a representative of the study site. The CRC creates retention strategies that might be adjusted to each participant, increasing motivation for both participants and consequently the study team. The strategies can range from a phone call between visits, to the creation of official letters to express appreciation for the participation in the study so far. Waiting periods and visits can be very time consuming and sometimes tedious, so an involved and proactive CRC will make the difference.

Source Documents and Electronic Case Report Form (eCRF)

A clinical study's success depends entirely on the quality of the collected and reported data. Therefore, it is essential that all study procedures and patient information (Source Documents) are adequately collected, documented and archived – an experienced and committed CRC is essential.[17] Subsequently, it is mandatory that all patient data are well introduced in the CRFs/eCRFs to minimize discrepancies and queries, and ultimately guarantee that data are accurate, and the reported results are credible.

Query Resolution

All studies are monitored and/or audited. Often the sponsor may send a study monitor, also called Clinical Research Associate (CRA), to review the study-related data. There may be discrepancies between the CRFs/eCRFs and the Source Documents, requiring clarification or correction – query resolution process. The CRC is the ideal person to support the study monitor in these procedures, solving the queries and facilitating communication and discussion with the PI and investigators whenever required.

Serious Adverse Events (SAE) Reporting

SAEs experienced by study participants must be reported promptly to the IRB and appropriate regulatory authorities. Guidelines for SAE reporting are typically outlined in the protocol document. The CRC is responsible for drafting the report and collecting all information, which is then reviewed and signed by the reporting investigator. The signed SAE report is then submitted to the IRB and other relevant entities. The CRC is also essential in ensuring the deadlines are met.

Drug Accountability

The study monitor performs drug accountability. This is done at the time of the monitoring visit with the investigational

pharmacist. The CRC may be responsible for scheduling visits with pharmacy staff and facilitating the communication between sponsor and pharmacy, as well as frequently being a bridge between the pharmacy and the PI and the remaining research team. Medication dispensing and it is delivery to the participant should be done by the pharmacist. Nevertheless, sometimes the CRC may be responsible for medication pick-up at the Pharmacy and delivery to the participant. In cases like so, all these steps between medication dispensing at Pharmacy and the delivery to the participant should be recorded in a study-specific log archived in the Investigator Study File (ISF)

Management of ISF

The CRC is responsible for maintaining the regulatory binder (ISF), which includes documentation of everything study-related, from time of submission to completion. These binders should be of restricted access, based on a role and authorization description, defined by the sponsor and/or investigator beforehand. As the binders have confidential information, the storage and access circumstances need to be adequately pre-defined by the sponsor, investigator, and institution.[30] Generally, the sponsor provides these binders. The ISF must be permanently up to date.

Central Laboratories

Many studies include central laboratories to standardize the analysis of medical images, or tissue, urine or blood samples. The CRC may be responsible for making sure that sample collection follows protocol, appropriate materials are used, and samples are properly labelled, documented, and stored. Additionally, the CRC may be responsible for the collection, processing, and shipping of the biological material to a Central Lab, when applicable.

Monitoring Visits Preparation

During the life of a study, routine remote and onsite monitoring visits are planned. Depending on the type of study, the types of monitoring visits will vary. A study that comprises a higher risk will require a monitoring plan that responds to those particular needs, and that plan is previously defined. Although the visits will be adjusted to the study at hand, the main objective of the monitoring visits is always to ensure the safety of the participants involved, that Good Clinical Practice (GCP) and protocol are being followed and the best and most accurate data are being collected.[31] Monitoring can be held either by the sponsor or its representatives, and monitoring visits are the perfect opportunity to guarantee everything is in order and prepared for an inspection or audit.

Audits and Inspections Preparation

Other visits that occur during the study course are audits and inspections. These are similar in some points, and both have the intent to show compliance and identify opportunities for improvement. An audit is a systematic examination performed by a competent sponsor representative, independent from the study, and is separate from sponsor-conducted routine monitoring and quality control. The frequency with which it happens is, again, dependent on the risk associated to the study. Compliance of the overall trial with protocol, GCP, sponsor standard of procedures and regulatory requirements will be accessed, and it will be evaluated if data were recorded, analyzed and reported accurately.[31] These visits will obey a standardized checklist, in order to improve consistency and harmonize expectations.[32]

An inspection is a review of documents, records, accommodations, and other available resources – including study site, sponsor facilities, contract research organization facilities or other deemed appropriate establishments –, carried out by the competent regulatory authorities.[31] In Portugal, inspections are conducted by INFARMED Infarmed. These visits aim to ensure that study-related obligations and data acceptability are maintained.

The CRC will help both the sponsor and the research team prepare for these visits, as a great deal of documentation will be needed – selection and organization of required material for visits is very time-consuming.

Conclusions

Besides lack of time and specific training from investigators and research team, the major limitations to the efficiency of clinical research worldwide include insufficient patient accrual and delays in trial activation,[33] as well as other factors of administrative or organizational nature, which are most of the times very time-consuming. And although lack of funding is still pointed as one of the main difficulties encountered with the conduction of clinical research, greater operational efficiency (streamlining and centralizing administration), improved trial design and having specialized personnel coordinating trials are some of the most frequent recommendations to reduce trial costs.[33] Thus, it is mandatory to guarantee an efficient organization and management of the study site.

One of the possible solutions is the implementation of a CRSU and the integration of a CRC in the research team. Clinical studies imply a disciplined approach to the care of the patients enrolled on the studies, and a "multidisciplinary research team" method is ideal.

Since the high performance of every member of the research team is crucial for developing excellence in research, training

and qualification should be compulsory requisites. Thus, the CRSUs should stimulate and support the certification of investigators and the research team in clinical research. CRSUs should aim to fuel the creation of highly motivated and organized research teams, focused on complying with all applicable legal requirements, and the greatest ethical and quality standards. The CRSUs ought to implement a quality management system in order to support the activity of clinical research centers, promoting their growth, and efficiency gain and leading them to a reputation of excellence in clinical research – whether it is sponsored by the pharmaceutical and medical devices industry or investigator-initiated.

Nevertheless, it is important to keep in mind that the PI is the one responsible for the conduct of the clinical study. Sometimes the PI tends to also delegate purely clinical activities to the CRC, which must be exclusively conducted by PI and Co-investigators. Another situation that should be avoided is the study monitor, from the sponsor or a sponsor representative, establishing "exclusive" contact with the CRC, forgetting that the main responsible of the study is the PI.

The CRC does have a crucial role in the conduction of clinical studies, and the qualification of individuals with adequate skill-set should therefore be encouraged. The presence of a CRSU with a competent CRC carries many advantages to the study site, not only facilitating industry-sponsored research but also enabling investigator-initiated studies. Many obstacles encountered in conducting the latter include regulatory submissions, training of personnel, and lack of statistics, data management and medical writing expertise.[34] An already existing CRC in the center, that perhaps mainly deals with industry-sponsored research, will help overcome these pragmatic challenges and allow for physicians to conduct their own studies. These seem to be extremely gratifying for the investigator,[34] and will allow the increment of local investigator-initiated research.

Furthermore, a strong CRSU gives rise to efficient, quality research, which in turn leads to improved, optimally delivered healthcare services,[1,35,36] improved outcomes,[1–5,37] enhanced infrastructures,[38] job creation, and cost savings (on the standard of care treatment),[39] retention of outstanding staff,[35] and an increasingly positive impact in the Portuguese economy.[40] In assessing the risk–benefit ratio, investing resources in CRSUs and their CRCs seems a low risk, high benefit answer.

Further studies on the medical, and socio-economic effects of high-quality clinical research activity in Portugal are both justified and necessary.

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IC and FF: Concept, manuscript structure and draft, information selection, review and final approval
MN: Bibliography, text writing and final approval
SS: Data collection, review and final approval
CG: Data collection, graphing and final approval
FP: Revision and final approval

Declaração de Contribuição

IC e FF: Conceito, ideia para o manuscrito estrutura do texto, selecção de informação e revisão
MN: Bibliografia e redação de texto
SS: Recolha de dados e revisão
CG: Recolha de dados e elaboração de gráfico
FP: Revisão

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