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Review Article

Quality Assurance and Associated Challenges at the Resource Limited, Rural Research Site

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Abstract

Clinical trial oversight is a critical element in clinical research conduct, it ensures the protection of research participants and the integrity of study data. FDA governs clinical research. Several key parties contribute to and work with complementary coinciding responsibilities such as study sponsor, research site, IRB, independent monitoring committees, contract research organization, and site management organization as applicable. The efficiency, and knowledge coherence to guide and direct each other among these groups is crucial for the successful conduct of a clinical trial. Challenges lie in this area of fields in various aspects. In this paper, the researcher has reviewed several elements at the research site with particular emphasis on resource-limited research sites. The researcher discussed some of the strategies to achieve quality conduct of clinical trials while achieving significant study enrollment at the resource-restricted research sites.

Keywords: Quality assurance; Clinical trials; Clinical research; ICH-GCP guidelines; Monitoring; Clinical trials oversight; Resource-limited research site; Rural research site.

Abbreviations: CFR: Code of Federal Regulations; CRA: Clinical Research Associate; CRC: Clinical Research Coordinator; CRO: Contract Research Organization; GCP: Good Clinical Practice; DMC: Data Monitoring Committee; DSMB: Data and Safety Monitoring Board (DSMB); EDC: Electronic Data Capture; FDA: Food and Drug Administration; ICH: International Council on Harmonisation; IRB: Institutional Review Board; NIH: National Institutes of Health; SMO: Site Management Organization; SOP: Standard Operating Procedure; VA: Veterans Affairs.

Introduction

ICH-GCP guidelines ensure that research study subjects are protected and that the study generates high-quality and meaningful study data. Originally, ICH-GCP guidance was established while considering contemporaneous good clinical practices of

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the World Health Organization, European Union, United States, Japan, Australia, Canada, and Nordic countries, with the aim of providing integrated quality standards to European Union, Japan, United States to expedite a communal acknowledgment of clinical data by respective clinical trial bodies [1].

These guidelines standardize the conduct of clinical trials and provide the regulatory structure for monitoring. The advancement of various tools such as electronic data capture system pushes for the further developments, example, centralized monitoring, remote monitoring, and decentralized trials updating the ICH-GCP guidelines to incorporate the requirements. The updated guidelines enable the execution of improved and more efficient approaches. It ensures that the standards are met for the following things: clinical trial design, trial conduct; oversight, recording, reporting, human subject protection, the integrity of trial data, consistency of study results, electronic records, and essential documents. The quality management is extremely crucial throughout the stages of the clinical trial, and it includes the design of the trial protocols, tools, and procedures for the data collection, data processing for the sound decisions. The sponsor is responsible for the establishment. of quality assurance and quality control systems and for ensuring that the trials are conducted, study data are generated, documented, and reported in compliance with the protocol, good clinical practice, and the applicable regulatory requirements. To ensure the quality in all phases and levels the study sponsors establish various measures, which includes providing appropriately qualified medical professionals to advise on the medical inquiries related to the trial or difficulties associated with the trial Design. Even though sponsor delegate individual study responsibility to Institutional Review Boards (IRBs), Contract Research Organizations, Independent Safety Monitoring Committees, and Site Management Organizations, their functions overlap with each other.

a. Institutional Review Board (IRB) is an independent body consisting of medical, scientific, and nonscientific members with the obligation of ensuring the protection of the rights, safety, and well-being of the clinical trial participants. The IRB approves initial protocol, continuing review, and subsequent protocol amendments, also, the methods and materials used during clinical trial conduct [2].
b. The Data and Safety Monitoring Board or Monitoring Committee (DMC) is an independent committee to review study safety data, critical efficacy endpoint, continuing rationality, and scientific ability of the trial at periodic intervals. DMC recommends to the study sponsor to modify, stop, or further continue the trial. Most DMCs consist of clinicians with relevant clinical expertise and at least one biostatistician having knowledge of statistical methods and sequential analysis of trial data. FDA doesn't mandate the use of DMCs in trials except in emergency setting research studies exempted from the informed consent under 21 CFR

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50.24(a)(7)(iv). The most government agencies such as NIH and VA required to use DMCs in specific trials [3].

The study sponsors ensure that the trial is practicable and avoid needless complexity in study procedures and data collection. The study sponsors also ensure that the protocol and study documents are clear, concise, consistent and that the approaches used to monitor and maintain the quality of the trial are according to the inbuilt risk the study possess. The FDA recommended including a risk-based approach in the quality management system. The goal is to evaluate the risks at various levels, such as, standard operating procedures, computerized system, trial design, study data, interim monitoring system, and the study results. The identification and evaluation of error possibilities, ruling out their evident extent and the impact on the safety of the research participants, data integrity, and the reliability of study results is highly crucial.

Discussion

Quality assurance at the research site

The quality assurance process at the research site focuses on areas such as; monitoring of the study participants right and safety, quality of study data, informed consent procedures and associated documentation, inclusion and exclusion criteria verification, ensuring real-time safety monitoring performance, the accuracy of the study visits, study procedures and related documentations, review of regulatory documentation which includes training logs, delegation logs, credentials, compliance with the study protocol, documentation of clinical judgment for study subject's safety and documentation of study related decisions, etc. In the current era, targeted risk-based monitoring proved cost-effective and attractive instead of time-consuming routine monitoring visits. However, complete source data document verification and onsite monitoring is still critical due to several reasons the researcher will discuss ahead [4]. Expecting the quality of the clinical trial conduct could be an ideal goal at the Research site, achieving the goal could be challenging due to several reasons, such as; challenges in finding experienced site-level research professionals, staff turnover, layover period among old and existing research staff dedicated to the study, the time needed for the new staff to catch up and understand the pending study related tasks such as study visits, data entry, quality issues or resolve monitoring findings, etc. Such unanticipated challenges may continue to meet high-risk criteria and require risk-based active significant onsite monitoring. Having onsite monitors always adds value by recognizing various areas that need improvements.

A risk-based plan, therefore, should include a combination of central monitoring and various-intensity local monitoring at the research site. To ensure quality clinical trial conduct and integrity of study data though the sponsor implement strategies for quality management, the best system for achieving quality at the research site relies on the site level, and it could serve as the preventative and proactive approach of the quality management [6,7]. It has been observed that the ongoing quality issues and related preventive-corrective action plans can serve as the teaching tool to the site personnel,

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however, it is not a solid permanent solution to improve quality at the research site. The establishment of the robust quality assurance system along with its ongoing maintenance, prospectively identifying site's internal quality issues, evaluating the root cause of the problem, thereby modifying, and implementing new improvement processes are required for the long-term consistent success [8]. Some of the steps to achieve the highest quality at the site are robust training and related resources. Establishing a common learning share folder with training materials such as study protocols, individual study training materials, which could be easily accessible to the research staff without restriction, dedicated trainer, dedicated experienced research staff, dedicated non experienced staff with the attitude of willing to learn, who can nurture and invest their time in reading, attending and practicing various training materials, and implementing strategies for the self-training while using the provided resources.

Other resources include a quality Control checklist, dedicated staff for checking critical items such as study eligibility criterias, SAEs, Investigational Product related documentation, study conduct, evaluating the quality issues and the reasons, so that the site staff can be retrained while recognizing their strength and deficiencies. The study sponsor's proactive and preventive approach at the early stages could prevent significant risk to the data quality and trial integrity. Once studies start recruiting, risk becomes an additional task that needs to be managed. Therefore, consideration of potential challenges ahead of time can be very beneficial to the success of the trial [9].

Quality assurance and associated challenges at the resource limited rural research site

Resource-limited sites could have significant patient populations and less competition; however, they may have some challenges such as, research ignorance among general population hindering clinical trial participation, difficulty in maintaining the quality of the research studies due to lack of the experienced research professionals, difficulty in expanding the research network due to the staffing issues. A proactive and preventative approach could save time and could be beneficial.

Example 1

Some research studies are very extensive and complex while some are difficult to enroll patients. Some may require additional assistance to recruit patients such as, conducting an advance routine lab testing to see if the subject could be screened for the study, this proactive step could avoid screen failure rate. The lab may or may not be part of the routine clinical care testing and it could add an extra burden on the research staff's busy work schedule to schedule the test.

Resolution

The research site could implement additional resources and strategies for those studies which has high screen failure rates, complex eligibility criteria such as long list of prohibited medications and required related research to prescreen the subjects, required study population having common but protocol exclusionary medical conditions, strict lab values etc. Sponsors should consider

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such challenges while negotiating the study budget.

Example 2

Study subjects referred by the third party may not have all the pertaining medical records available, and it could be time-consuming for the research coordinators to request medical records from outside healthcare facilities by making phone calls, follow up calls, fax, etc.

These tasks can place an additional burden on stressed research coordinators, leading to a lack of enthusiasm.

Resolution

While considering the additional assistance or resources to be provided to the research coordinators, the study budgetary constraint and questions come into the picture. Does the study budget is sufficient to recruit additional resources while considering the study enrollment challenges? Does the budget justify the efforts site is putting into difficult to enroll or complex study? Typically, the study budget has the provision for the ongoing resolution of EDC queries in long-term observational studies, or for the long-term follow-up period of the interventional studies. Does the budget have the provision for the maintenance of the studies which have no enrollment for an extended period, or studies with very few yearly onsite study visits?

If the answers to these questions are "No," then the study budget requires an amendment. This is to make clinical trial recruitment, clinical trial conduct, and staff retention process easier at the research site.

Challenges for quality assurance from monitoring visit perspectives

Onsite monitoring with the restricted duration of 1-3 days may not be enough for the high recruiting studies. Having insufficient time spent by the CRA during monitoring could lead to bad quality review work. For the sites located at the distinct locations, CRA may be spending several hours to travel to the site and could end up spending less number of hours on the site for the actual monitoring work.

Resources available at the research site

It is critical to evaluate research staff workload while considering their research experience. Does the research staff have enough expertise to conduct multiple study visits for the multiple clinical trials and handle the number of study subjects with or without assistance? Such items require attention. Ideally, sites should have efficient, experienced study coordinators in place before the study begins, however, finding experienced research staff in resource-limited sites is a considerable challenge. Having a restricted study budget on top of this challenge is a big crunch in the current competitive job market. The sponsor needs to consider this aspect while negotiating the budget with the site while also acknowledging the benefits of getting diverse needy patient populations in a rural geographic area. This is an opportunity to make a significant contribution to the drug development and ultimately to the society. All these described factors can directly or indirectly affect the quality conduct of the clinical trials at the resource limited sites.

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Typically, the research sites conduct multiple clinical trials with multiple study sponsors and resource-limited sites are no longer exceptions to this. Site staff may have several tasks on their to-do list such as study visits, data collection and reporting, recruiting new subjects, accommodating various monitoring visits adding to the workload of the already busy staff. These factors without enough assistance can affect the quality of the clinical trial at the high enrolling sites, thus the need for harmonization among trial sponsors and the availability of sufficient resources at the site is critical to achieve compliance with the ICH-GCP guidelines.

The availability of well-trained research staff and staff with an attitude of "Willing to learn, willing to be trained and willing to run an extra mile in order to excel" is the demand of the time and key for the successful research site, however the most challenging task is to find such candidates and its ongoing search in the laid-back rural areas. Clinical trial conduct-related training and simultaneous motivation can be provided to the unexperienced candidates; however, certain things cannot enforce, which are "Reading interest, implementation of logic for transferring the knowledge gained from one aspect of the trial to another aspect of the trial or utilization of research knowledge gained from one trial into another trial, multitasking, critical attention in details, proactive steps, and prolonged strategic reading".

Having availability of experienced staff is always beneficial, however in rural areas, it is tough to find experienced CRCs. This is because, there are plenty of scientific, non-scientific, non-stressful employment opportunities are available, which can attract emerging new professionals to pursue further, such as, medical assisting, various medical specialty technicians, nursing assistants, nursing, physician assistants, pharmacists, pharmacy technicians, doctors, human resources professionals, teachers, teaching assistants, local businesses, etc. So, pursuing the emerging candidates to engage in brainstorming research work which requires constant reading, thinking, and developing other critical skills is a challenging task, if not impossible in the laid-back area.

Maximizing staff remuneration, demands, and opportunities

Plenty of remote and onsite clinical research Job opportunities in CROs, SMOs, research institutes, academia, and the pharmaceutical industry are, attracting experienced research professionals at the field level, which makes retention of staff at the research site difficult. Currently, industry research jobs are attracting experienced research professionals, creating a deficiency of these skills at the site level. This makes the sites to train and invest in new unexperienced personnel, however, by the time unexperienced person becomes experienced, sites need to be prepared to lose them for the candidate's opportunity of the dream. Due to current trends, not only rural locations with limited resources but also research locations with available resources have been significantly affected.

Challenges in maintaining quality at rural research site

Staff turnover is increasing due to the lucrative opportunities available in the industry. Lack of commitment among entry-

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level professionals due to the availability of the plenty of relaxed, easy-going, easy work schedules, non-brainstorming job opportunities.

Unavailability of experienced clinical research professionals

- Poor study budget makes it difficult to hire or relocate experienced professionals with competitive salary similar to the industry.
- Mediocre CRAs with no prior study coordination experience are unable to understand the site-level challenges, field-level challenges, and protocol complexities. Difficult or complex study protocol and study visits can take much manpower, burnout research coordinators, inexperienced study staff with lack of enough expertise fuels up with lack of preparation, strategies, and readings, noncompliant patients missing study visits due to long-distance commute distance.

  It is important to be realistic about target enrollment while looking at the resources.
- The study sites must modify the research conduct and recruitment strategies according to the goals and circumstances. The same strategies may not work for all the studies all the time.
- Negotiate a great study budget with the study sponsor while proactively looking at the challenges and success rate to avoid future quality issues and failures.

For study sponsors-things to consider

Negotiate a sound study budget with the sites while considering the challenges and pros of conducting the trial in the diverse needy rural population, thereby helping the sites to develop clinical research professionals and staff retention. Quality assurance becomes an easy task with staff retention, competitive salary, and dedicated research staff.

- Helping the sites in recruitment efforts for difficult-to-enroll protocols.
- Fully understand what a research site can offer while considering the challenges and the benefits of providing them enough resources.

For research sites

Things to consider

- Provide great benefits, competitive salaries, motivation, encouragement, and support systems to the existing and budding clinical research professionals. Develop and provide accessibility for the excellent training materials and associated resources to the research professionals. Encourage and expect ethical clinical trial conduct.
- If finances permit, retain permanent quality assurance personnel and designated trainers as an additional resource to the research staff.

Nothing can replace clinical research experience

- It's essential to invest efforts in developing the right personnel so research conduct and associated

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knowledge can pass on in resource-limited sites.

- Conducting a clinical trial and gaining related work experience is not a short-term endeavor, in the long term it creates a compassionate, multitasking science-curious research personality.

For new research professionals, things to consider

It is worth choosing clinical research as a career but be ready to invest time in developing critical skills, such as, reading, key attention in details, strategic thinking, excellence, multitasking, prioritization, "Work Hard and Play Hard" attitude, cultivating research logic and implementation. Read and understand clinical trial protocols, clinical trial rules, regulations, ICH-GCP guidelines and concepts.

Implement strategic knowledge learnt from the past studies into the successful conduct of the new studies and gain hands-on experience.

Experienced research professionals, things to consider

Contribute to spreading clinical research knowledge, accessibility, and availability in resource-limited rural patient population. Spreading research knowledge and expertise among fellow healthcare professionals and new research professionals.

Contribute to the development of research infrastructure in unique rural communities, contribute to the creation of clinical research employment opportunities, develop new clinical research professionals, and reduce the lack of required skills in resource-limited sites.

Conclusion

Researchers often see a variety of research articles in various journals about successful clinical trial conduct, related study design, study results, and more. There are hardly any articles published on this critical topic, which is "Quality assurance and associated challenges at the resource-limited rural research sites." Given the advancements in medical science and the drug development process, the need to spread research awareness and interest in rural areas is of paramount importance. The ultimate goal is that data from all walks of life should be well presented in the results of clinical trials and serve the products it serves.

The researchers believe that this topic requires further attention and intervention as it involves a diverse patient population from rural or medically underserved geographic areas. The quality assurance and monitoring of the clinical trial is no longer a challenge at resource available areas, however, it could still be a considerable challenge in resource-limited research sites. The study sponsors' indirect assistance while considering this challenge can help and motivate the research sites in maximizing their potential. The demand of the time is, needy patient population, the opportunity to develop research infrastructure in resource-limited sites, increasing research awareness in patients and in general population, creating new job opportunities etc. Government assistance and subsidies for the rural research sites could be beneficial, and this aspect requires further detailed discussion!

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