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Organizing a Clinical Trial for the New Investigator

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Abstract

Background and purpose: Clinical trials organization can be daunting especially when orienting to a new system. The steps to a successful clinical trial are not concrete and vary based on the system.

Methods: In this section the discussion centers on how to shape the question for the clinical trial which is rational and feasible to answer within the planned study design.

Findings: Senior mentorship, collaboration and early involvement of stakeholders can help shape a successful clinical trial. Keeping in mind ethics and the processes within a system will make planning easier. Questions about key elements of the trial should be answered early to prevent delays of study initiation.

Conclusion: Clinical trial development and implementation can be very rewarding, but successful outcomes require careful planning and considerations.

Keywords

Clinical trials

Introduction

The aim of this paper is to help a new investigator be aware of the many steps needed to initiate a successful clinical trial. In addition many of the pitfalls of clinical trial planning have been included to help avoid these at the initiation of a new clinical trial.

What is a clinical trial?

The definition of a clinical trial varies by the source. The National Institute of Health defines it as: involving one or more human subjects, the human subjects are prospectively assigned to interventions, the intervention effect is evaluated in the human subject and there is an expected health-related biomedical or behavioral outcome.(1) Clinical trials span a wide range of topics including questions answered using any of the following methods: mechanistic, exploratory/developmental, pilot/feasibility, interventional, or behavioral.

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How to formulate your question?

This seemingly simple beginning to planning a clinical trial can pose great difficulty if not well thought out at the onset of the early clinical trial organizational phase. The first step in the process is to formulate the question you want to answer. Part of the question formulation process is to perform a comprehensive literature review and search of the current registered clinical trials. Importantly, the question posed should serve as the basis of why the clinical trial is being done. This should motivate not only the investigator, but also those the investigator is seeking to attract (e.g., grant agencies, pharma, etc) to support the concept. If the question answers why the clinical trial is of importance, the details pertaining to how the study be done and what is being measured will follow. The question and hypothesis should be a framework for the entire study and help further plan the study design.

Once the concept of the clinical trial has been formulated, further definition of the question should take place by seeking out opinions and confirming the approach is in-line with the group consensus vision, addressed in more detail later in collaboration section. If the question does not fit with the vision of the group then the support for a new investigator will likely waiver and hinder the success of the clinical trial. The importance of mentorship from a senior investigator cannot be over emphasized. A senior investigator can help the new investigator differentiate the specifics of the question being evaluated, for example, whether the question should be asked about the newest drug or a particular drug. Mentorship on study design to appropriately address the question is also key in the development of a clinical trial for a new investigator. Common pitfalls can be avoided with asking the question in the right way and early mentorship from senior investigators. A senior mentor who has developed and overseen clinical trials over the years can not only help craft the language of important elements such as the trial's primary objective but can also serve as an advocate for the new investigator as (s)he runs the gauntlet of objections from other investigators or colleagues. Often, the most important advice from the senior mentor is (1) when to amend the trial and (2) when to stay put with the trial as designed.

What is the rationale and feasibility of your study?

The rationale should be involved in the question forming process and should focus on how to improve outcomes of the condition/disease. A common mistake is to have the rationale or preliminary data be too supportive of the drug or intervention being tested or testing something that is already part of a standard of care. For example, if the study is planned to be a randomized controlled trial, subjects need to be willing to participate and find it acceptable not to receive the intervention or only have the opportunity for the intervention if randomized to the treatment arm incorporating that therapy. Most patients and stake holders would find it acceptable for the control subjects to undergo the current standard of care. Involving patient advocates from local or national organizations can increase the chances of designing a study that will be accepted by patients. (See essay 6 in this issue from Rick Bangs and Tony Crispino)

Feasibility is critical in the development of a clinical trial. It is important to characterize the population being studied, limit heterogeneity while still being pragmatic in the design; this is

especially important as investigators are re-examining trial exclusion criteria that may reduce the generalizability of the study. The population available, incidence and event rates will help determine the study design. Characterization of the at-risk population and demographics can help determine the trial's feasibility. If a similar study has previously been successful, the feasibility of the study can be easily determined. If previous studies in the same population have failed, under the same constructs, then investigation into the pitfalls of the previous study may help in refining the study design. Special consideration of the follow up should take place during the initial design phases and in creating appropriate endpoints. Follow up needs to be feasible with the staff of the study and for the patients. Creating a follow up plan that is most consistent with standard of care approaches is best when designing the study, especially when considering what elements of the trial will be covered by insurance or other payers.

The emphasis on study design and evaluable data is important. Involving a biostatistician early is essential and, for experienced investigators, mandatory. Biostatisticians can help with power calculations and whether the trial should be carried out as a superiority or non-inferiority trial. Considerations in the study planning depend on the feasibility. If there is a small population to be studied (e.g., rare diseases), the study design may include a single arm or may require multiple study centers. If feasibility is questionable, a pilot study can be helpful to provide confidence to both collaborators and funding agencies that the final trial will be successful. A pilot study can help generate preliminary data as well which can attract stakeholders and funders.

Other questions about feasibility which should be addressed is whether the trial is technically and monetarily feasible. The technical feasibility will depend on the facilities available, environment and equipment needed. If a core facility is needed for the study is it easily accessible? Is the group environment supportive of the trial? Where will samples from the study be stored? All of these questions help to answer if the current clinical trial design is technically feasible.

It is equally important to know if the study is monetarily feasible? Creating a preliminary budget early on with an experienced grants management officer at your institution or group can help determine what funding is needed to complete the clinical trial. If funds have been set aside for the trial, such as seed money, grants, endowments or philanthropic contributions, it will be important to investigate the stipulations of use of these funds. It is similarly important to ensure that institutional overhead costs (indirects) are included. There is always an expectation that the budget will undergo revision, but a general understanding of monetary feasibility is important at the trial's outset. Making sure appropriate staff are added into the budget early on can help with hiring and accurate budget appropriations.

Who are the important stake holders and collaborators?

Although fourth in order in this article, this should be accomplished at the onset of the study. Co-investigators, collaborators and stakeholders can be important resources to develop generalized enthusiasm for the clinical trial. Involvement of the key stake holders will also

help formulate a better question. If there is uncertainty about who should be invited to collaborate, advice of a senior mentor can help with the process.

With a successful collaboration, the clinical trial begins to be plausible. The cautionary tale with this principle is to make sure the collaborators will contribute to the group and will help the new investigator develop the foundation for a career with the work done in this clinical trial. Establishing clear roles, plans for evaluation and analyses of clinical data and translational projects, and publication plans early prevents confusion and disappointment surrounding an individual's return on investment of their time.

Ethical considerations

If the question being asked already has an acceptable treatment available with low toxicity it may not be considered ethical to test this against a treatment of questionable benefit with a high toxicity. Important considerations include the following: Will the study alter clinical practice in a meaningful way? Will it be beneficial to the patient? Is the patient being put at risk if the treatment being considered is not effective in the disease state? Is there evidence of disease effect from the treatment being considered? If there is any question in the ethics of the clinical trial this can have serious deleterious effects on not only this clinical trial, but also any future trials.

Additional ethical considerations for clinical trials include if animals are being utilized for any reason. It is also important to make sure all the staff have human, animal and lab training required by both their own institutional and by any other regulatory bodies. Involving an ethicist if there is any questions of ethics during the planning phase may be helpful.

Should the clinical trial include a biorepository?

If the clinical trial has a limited budget or if planned future use of trial specimens a biorepository can be a great resource to investigators. A biorepository may already exist within the institution and collection of samples for the specific patient population may be useful for future studies. Creation of a biorepository does take considerations of space, money and personnel all needed to establish the repository, particularly if there is not already a mechanism for this at the institution. If the study is multicenter, discussion of where the samples will be housed, how they will be collected, and what is to be shared is prudent in planning of the clinical trial. Providing specimen collection kits for set time points and planned batch shipments can avoid confusion about sampling and save money for shipping specimens. Material or data transfer agreements are essential (and, sadly, often overlooked). These agreements are necessary in order to share specimens or de-identified patient data. These agreements can take several months to develop and should be considered at the onset of the study to avoid delays. It should be noted that there are very organized and quality biobanking efforts that can be used for National Clinical Trials Network groups such as Nationwide Children's which serves as the biorepository for SWOG. (2)

What parts of system(s) where the study will be conducted should be involved?

There are many moving parts to the research systems and deciphering the critical parts can be tough. Once all the parts of the system are identified maintaining communication is key. Many systems issues can arise and the following questions should be considered while planning a clinical trial: Do you have the proper protocol for the regulatory body data collection? How will the data be collected, entered and secured into the system? Who will monitor for adverse events and enrollments? Should you empanel a Data Safety and Monitoring Committee to monitor the study? What approvals are necessary for your trial to move forward and what is the necessary oversight for the trial? What FDA approval for a drug or device is needed, or is it minimal risk and a waiver is likely to be approved. If there is an investigational new drug (IND) application who/what group can help with this application? Do you have an IND monitoring office locally? If the clinical trial is a multicenter study how will the grants and contracts be administered? What are the technology challenges? Are there any competing interests? Can you work with the electronic health record to ensure easy data collection or should you develop your own data management system for the trial?

Industry relations

Industry should be a partner, not the principal investigator. The partnership should allow the clinical investigator to remain academically objective. Make sure the interests of the investigator and institution are protected. A key to leading the partnership with industry is reserving the right to perform the data analysis, retain the samples and write the manuscript without industry oversight. Industry collaboration can be very beneficial. A caution is that if there is not a local champion for an industry study then it is unlikely to be successful.

Is the study integral or integrated?

This question becomes important when applying for funding from the National Cancer Institute (NCI). Integral focuses on biomarkers and integrated correlates biomarkers with outcomes. (3) Determining the answer to the question can help you with study design and potentially increase funding opportunities.

Summary:

Clinical trials development can be daunting especially when orienting to a new system. The above questions are just a few to help the new investigator plan and deliver a successful clinical trial. By no means is this an expansive list, but the questions asked above should help shape a formidable inquiry with a feasible research plan leading to a successful clinical trial initiation. The over-riding key principle is to actively engage with mentors and research staff with the experience to assist with the individual institution’s requirements. Starting out with a small pilot study is an excellent way to begin to learn to navigate the system and develop a clinical trials research career. Experience generates collaborations and relationships that make subsequent endeavors more feasible.

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