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Are clinical trials complex projects?

Lester Raymundo Dominguez Huarcaya[1], María Fernanda Dominguez Ríos[2], Mohammad Reza Mohammadi[3*]

[1]*Faculty of Pharmacy and Biochemistry, National University of San Marcos, Lima, Peru*
[2]*Faculty of Psychology, Pontifical Catholic University of Peru, Lima, Peru*
[3]*Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

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ABSTRACT

Clinical trials are research projects that are performed on human subjects to determine the efficiency of certain medical or behavioral interventions or therapy. This review will focus on a few of the most critical differences between straightforward projects and those that include a higher level of complexity. A complicated endeavor can have a variety of connotations for various individuals. One further measure that may be utilized to quantify the level of complexity that the task entails is the number of individual interactions that are necessary to complete it. The greater the number of functional units that interact with one another, the more complicated the integration will be. When functional units are dispersed around the globe and when differences in cultural norms make it difficult for them to interact with one another, things can become complicated very quickly. When the scope, cost, and length of the project are all larger, it is more likely that changes in the scope will influence the budget and the timeline. Cost and time overruns are more likely to occur in clinical projects that are larger and more complicated. The co-clinical projects decrease the disparity available between pre-clinical investigations and clinical trials. Emerging data such as artificial intelligence from closed sub-protocols have the potential impact on the conduct of ongoing studies in the case of biomedicine and nanomedicine. Furthermore, in this review, we have discussed current nanomedicine in the clinical stages.

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Introduction

We need to get started by defining exactly what it means when we talk about a project. Much of the time, undertakings are one-of-a-kind endeavors that have never been attempted before and are highly unlikely to ever be attempted once more. There is never any ambiguity regarding when a project will start and when it will wrap up. Although it is possible that certain projects will be exceedingly like one another, even to the point of being identical, and will involve a substantial amount of repetition, it is more probable than not that these occurrences will be the exception rather than the rule. Given the one-of-a-kind nature of projects and the activities that are associated with them, it is probable that determining the quantity of work necessary to finish a project will be extremely difficult, and the estimates that are created may not be particularly reliable. This is because projects and the activities that are linked with them are unique. This may present the functional manager with certain challenges and issues to deal with [1-3].

Every project is subject to a certain constraint or limitation of some kind. The most common kinds of constraints include time frames that include predetermined milestones, financial limitations, and quality restrictions that are outlined in the specifications [4]. The common constraint may be the risk tolerance of the project team or the owner, as well as the amount of risk they are willing to endure. This limitation can also refer to the amount of risk they are willing to tolerate. Moreover, there is the possibility that the quantity, quality, or degree of expertise of the resources that are necessary to finish the jobs will be limited in some fashion. The phrase "resources" can apply to both the living people who offer the labor and support as well as the inanimate things, such as

*Corresponding author. E-mail: mohammadi.mreza73@gmail.com

buildings and financial assets, for example. It also refers to the people who supply the labor and support [5].

There are numerous ways in which complex projects are distinguished from standard projects; several of these ways are illustrated in the feature that can be found below. There are many ways in which a complicated project might be described [6]. The number of interactions that must take place for the work to be finished is another way to characterize the complexity of the situation. The integration process is made more challenging whenever multiple functional units are required to interact with one another. It is a significantly more difficult challenge to solve when the functional components that make up the problem are dispersed all over the world and when cultural differences make integration impossible [7]. The complexity of a problem can also be determined by its size and length. The greater the project in terms of scope and expense, in addition to the lengthier the time, the greater the likelihood that scope revisions will occur, which will affect both the budget and the schedule. It is not uncommon for large and complicated projects to experience budget overruns and schedule delays [8].

Considering clinical trials as complex projects

Similar to other types of complicated treatments, clinical trials entail a large number of participants, procedures, and components operating on various levels [9]. In the same way that a smoking cessation program attempts to enhance participants' health by enrolling them in protocolized delivery of a smoking cessation intervention, a clinical trial seeks to improve participants' health by enrolling them in protocolized delivery of specific therapies. Certain fundamental aspects of these complex interventions must be carried out in the same manner everywhere, while other aspects, which are referred to as the malleable peripheral, can be modified to fit the requirements of individual settings [10-12]. Similarly, clinical trials are comprised of unique core components as well as a flexible peripheral that is included in a larger ecological system [13]. The protocol for the trial includes all the necessary components for conducting an approved clinical trial, such as trial design features (for example, the number of arms, the number of comparator arms, and eligibility criteria), are the same at each site to keep the comparisons constant and to ensure that the trial has internal validity [14]. The implementation of this protocol, on the other hand, is subject to significant variation depending on the locality. Even the process by which locations are chosen to take part in a trial and, as a result, become qualified to carry out the trial protocol can be altered in different ways depending on the kind of study that is being carried out [15]. Other variables, such as how trials are publicized to providers or patients, how possible participants are discovered, or how frequently enrollment objectives are assessed, are typically left out of the protocols for clinical trials [16]. Previous research on the conduct of clinical trials has focused almost entirely on the fundamental aspects of trials, such as the modification of protocols to increase the likelihood of clinical trials being successful by broadening the participant eligibility requirements [17, 18]. Even though these adjustments might be helpful, there is no assurance that clinical trials will be conducted at every site or that every possible participant will be reached by using them [19]. An approach to trial development known as implementation science can put further emphasis on the flexible peripheral that is accomplished by discovering and targeting tactics for the most effective execution of trial protocols in a variety of settings [20, 21].

Clinical trials are research projects that are conducted on human subjects for determining the efficiency of a certain medical or behavioral intervention or therapy is effective [22]. In addition, the co-clinical project can decrease the disparity that exists between pre-clinical investigations and clinical trials [23]. These projects are essential to the development of illness management because, when carried out appropriately, they give the evidence required for revising the standards of care that are already in place [24]. The enrollment of participants is critical to ensure the success of clinical trials; nevertheless, difficulties in meeting recruitment targets continue to be a problem [25, 26]. A study from 2018 found that although there is a diversity of ideas in the literature about interventions to boost clinical trial recruitment, they lack depth [27].

The challenges that are related to participant recruiting are multifaceted and numerous. They include things like characteristics about the protocol, the capabilities and resources of the site, and challenges that are

special to the participants [28]. Recruitment in some countries can be difficult due to the country's relatively small population. The problem is made much worse by the fact that treating clinicians and experts do not make nearly enough recommendations for clinical trials. Primary care doctors have a lower chance of having access to relevant trial material or evaluating patients for participation chances since general practitioners treat a wide variety of ailments without having any link to clinical research. This makes it less likely that primary care clinicians will examine patients for participation opportunities [29]. It is possible for insufficient recruitment to lead to underpowered studies, which in turn reduces the validity of the research outcomes and contributes to the delay in the development and implementation of essential new medicines. Insufficient recruitment causes additional expenditures to be incurred when initiating new trial locations, as well as delays in the trials themselves for the sponsors [30]. It has been emphasized supplying instructions that needed only minimal or no clearance from the sponsor or regulatory body. The purpose is providing sites with more autonomy and knowledge so that they are better able to evaluate, monitor, and proactively control the outcomes of recruitment efforts. The objective of the program is to gain an understanding of the challenges that are associated with site recruitment and to locate solutions at the site level that are both generally transferable and applicable. The investigation did not investigate concerns such as inadequate trial design, problems with participant retention, or a general lack of understanding regarding clinical trials. On the other hand, site-specific recommendations on how to raise public knowledge of a certain experiment were found to fall within the parameters of the project [31]. To keep the public informed about the significance of the trial, it is the responsibility of the trial team to coordinate talks and presentations on a local, national, and even international scale [32, 33]. Maintaining personal contact with a collaborative group of doctors is the most difficult challenge for a trial manager and the trial team, regardless of whether the group consists of seven or seven hundred doctors; nonetheless, overcoming this challenge will result in more coherent research [34].

A trial manager

The Health Technology Assessment (HTA) program of the National Institute for Health Research (NIHR) acknowledges that the appointment of a dedicated project/trial manager is essential to the performance of primary research studies [35]. Although it would be preferable to have trial managers involved in the design process from the very beginning, this does not generally ever happen because of financial constraints. A good trial manager, on the other hand, will have input on the design of the trial as well as the application for financing, which will help with the trial's practical components, such as conserving money and avoiding inefficient procedures [36].

Project planning

According to the definitions that can be found in the field of project management, a clinical trial is very similar to other types of commercial projects in many respects, but are not limited to a distinct goal to bring about change the requirement of a group of people, a defined time scale, identified resources necessary to accomplish its goal, and obligations that must be fulfilled (according to a requirement that has been set) [37]. Every project is made up of a string of procedures or a group of things to do to achieve certain goals. The five fundamental stages of the process include 1) starting, 2) planning, 3) executing, 4) keeping an eye on things and exercising control, and 5) reporting and statistical analysis [38]. According to the definition provided by the Clinical Trials Facilitation and Coordination Group (CTFG), a clinical trial is considered to have a complex clinical trial design if it is comprised of multiple independent clinical trials and/or extensive prospective adaptations [39]. Sponsors can designate study cohorts or arms within their protocols or within a shared protocol, which will be referred to as "sub-protocols" throughout this article, depending on the circumstances. In the context of the overall design of a clinical trial, sub-protocols are differentiated from one another since each one calls for its specific battery of statistical tests. On the other hand, the term "arm" will be used to identify study cohorts that rely on other cohorts for their statistical analyses, such as comparison to a common control arm. This contrasts with the use of the term "cohort," which will be used to designate studies themselves.

Each sub-protocol could contain a single arm or several different arms [40].

With a standardized operational framework for complicated clinical trial designs, it may be able to make the most efficient use of operational resources and assign trial patients to the sub-protocol or arm that is the best fit for them [41]. A centralized screening platform that ensures efficient operations and makes it easier to enroll patients is frequently at the center of designs for such complex clinical trials [42]. Either a screening platform and common operating structure can be detailed in a master protocol, or these components can be written within the clinical trial protocol themselves.

Potential opportunities and challenges of complex clinical trials

In the last ten years, there has been a substantial development in the application of precision medicine, notably in oncology research. In this field of study, enrichment designs drive immunotherapy drug candidates toward tumor-specific genetic modifications in sophisticated trial designs [43]. Therefore, the objective of medicine is to conduct drug tests solely on those individuals who stand the most to benefit from them. The clinical development process might be sped up with the support of this type of biomarker-driven development, which would also be beneficial to patients by helping to better match them with the anticipated best treatment option [44].

The availability of many investigational medicinal products (IMPs), populations, trial sites, a variety of manufacturers, and contract research organizations (CROs) all contribute to an increase in the operational complexity of such a trial [45]. Therefore, alterations may present challenges for both the investigator and the sponsor, placing at risk the trials' ability to monitor patients' safety and perhaps affecting the benefit-to-risk ratio of the trial [46].

Complex trial designs that propose extensive prospective adaptations, such as the addition of new IMPs or populations, pose a challenge to the regulatory framework of the European Union (EU) in terms of the definition of a clinical trial and the transparency of the data. This is in addition to the fact that these designs make it difficult to provide clear information, particularly to the people who will be participating in the trial [47].

The EU Clinical Trials Register makes available for general consumption a selection of the summary reports that have been published. Data transparency is a key concern for complicated clinical trials that are being submitted as one clinical study [48]. This is since the release of sub-protocol results will be postponed until after the main clinical trial has been finished.

The parallel testing of numerous IMPs on relatively few trial patients, the difficulties in preventing type I error, and the issues generated by shared control arms are all factors that raise questions about the scientific merit or outcome of sophisticated clinical trials and need to be dealt with head-on. Furthermore, emerging data such as artificial intelligence from closed sub-protocols have the potential to impact the conduct of ongoing studies, which raises issues regarding the integrity of data in intricate trial designs [49].

Key recommendations for initiating and conducting complex clinical trials

To guarantee the safety of participants and maintain the integrity of the research, a clinical trial needs to be carried out in line with ICH E6 (R2) and the EU Clinical Trial Directive 2001/20/EC [50]. If each clinical trial evaluates a different scientific theory, and the sponsor maintains appropriate control over the study's safety and integrity, then regulatory authorities in the EU and the European Economic Area (EEA) have no problem with the use of unique designs for clinical trials [51]. Before beginning and carrying out challenging clinical trials in the EU/EEA, the sponsors should conduct risk assessments to determine the potential dangers associated with (IMPs, trial demographics, and operational complexity [52]. After establishing methods for risk reduction, sponsors should consider the eight fundamental parameters that are listed in figure 1 [53, 54].

Over the past few years, there has been a discernible rise in the amount of international collaboration on clinical research. Collaborating with people who are geographically separated requires a significant amount of time and money and is riddled with challenges [55].

Unpacking the three dimensions of complexity

Complexity can be found in almost every therapeutic field, many trial sponsors, and a great number of studies that are currently being conducted [56].

Treatment, patient flow through the trial, and point-in-time complexities are some examples of the kinds of things that might be grouped under the umbrella term "protocol complexity" [57]. The use of personalized medicine, variable appointment scheduling, and several therapy groups are just some instances of the complexity of some protocols. Studies with high protocol complexity include single-blind and double-blind studies with re-randomization or adaptive randomization methods, as well as studies that add new ailment kinds as the trial progresses. Other types of research include trials that combine blinding approaches [58-60].

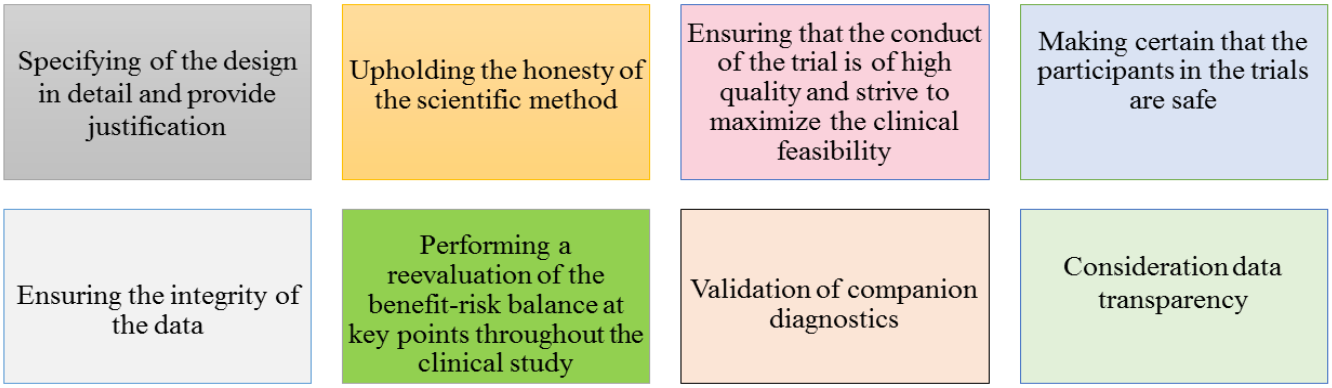

Fig. 1. The main parameters for suitable clinical trials [53, 54].

The term "operational complexity" refers to problems that develop throughout the process of actually conducting the research. There will be a variety of techniques taken to the supply chain, pharmaceuticals will be sent directly to patients, the project will have an international scope, and there will be extensive clinical research [61].

Complexity brought on by unanticipated change cannot be prepared for in the same way that complexity brought on by protocols and operations can be. Because trials are experiments, it is difficult to know for sure what will change, but we can be quite certain that something will. Unanticipated shifts in either the protocol itself (which may include several protocol revisions) or the operations themselves (which could involve the addition of a new country or region) could occur. The variables can be traced back to the origin of the complexity that is present in protocols, operations, and dealing with change that was not foreseen [62].

Complexity in real life: examples from Suvoda's portfolio

Each of the studies that Suvoda supports is tough in at least one way, and most of them are challenging in two or more ways. This is the case for a couple of different reasons: first, because we focus on challenging trials, and second since the great majority of trials that are now being conducted are complex in some way [63]. A significant number of studies, sponsors, and therapeutic areas use protocols that are highly difficult to understand. For instance, in a study for cancer treatment that had only recently finished and was of the open-label, phase I variety, multiple characteristics of protocol complexity were visible. Within this study's several treatment groups, various pharmacological classes from a wide range of pharmaceuticals were investigated and analyzed [64-66]. Different visit patterns are required for the various therapeutic combinations because there are a variety of possible dose schedules and cycle lengths that need to be accommodated. Because that this was a Phase 1b study, the enrollment dose strength for each medication type was also unclear at the beginning of the trial. The fact that their total number was never established was one of the factors that contributed to the difficulty of the subjects in this trial [67].

There is a degree of complication involved in the procedure as well as the operations of many investigations. Due to the nature of the study's design, for instance, another dose-tolerability study that is part of the early stage of cancer research and involves two investigational medications has a protocol that is difficult to follow. Multiple types of illnesses and treatment groups are now being investigated, in

addition to a dynamic cohort design, a flexible dosing schedule, undetermined dose strength, and an unspecified dose range [68].

A Phase 3 evaluation of a medication for a rare disease that covers numerous countries and sites is another study that presents significant challenges in terms of its operational complexity [69]. Late-stage clinical trials for uncommon diseases frequently require many sites. This allows researchers to maximize the possibility of recruiting patients who reside close enough to participate in the trial [70]. On top of the intrinsic complexity of the protocols and procedures, each of the four example studies had an additional layer of complexity added to them as a result of unanticipated change. In addition, there is always the possibility that unexpected changes will be made to the procedures and operations of the research, such as the addition or deletion of trial locations [71].

Implications: Effectively harnessing complexity to drive breakthrough results

Many oncology studies include coordinating multiple types of drugs, which may result in ongoing modifications to study demographics, dosing regimens, and therapeutic interventions [72, 73]. Additionally, intellectual property and standard-of-care therapies are frequently procured and provided in various methods depending on the study. Nearly all studies that have concluded their development stages cover more than one geographical location. Due to the complexity of this and other research, the trial's sponsor had to provide careful consideration to a diverse range of criteria [74]. When trials that involve complicated issues are managed using technologies designed for straightforward studies, this can, unfortunately, result in delays, increases in costs, and a more difficult procedure for sites to follow to carry out the study [75].

Clinical trials in nanotechnology

In 2014-2015, Food and Drug Administration (FDA) approved nanomedicines with 77 products in clinical trials and about 40% of trials listed in clinicaltrials.gov [13]. To 2021-2022, there are 563 in clinical process (663 in total: 33% in clinical phase I and 21% in phase II) and 100 nanomedicines on the market. Most of these nanomedicines are and mainly focus on infection (14%) and cancer (53%) treatments, which their information can be obtained from the Cortellis Drug Discovery Intelligence (CDDI) database. Furthermore, mental diseases, nervous system diseases, endocrine and metabolic diseases, immunological diseases, blood disorders, inflammation, cardiovascular diseases, ocular diseases, skin diseases, vaccine development, and imaging diagnosis have been improved by various organic and inorganic nanomaterials (Figure 2) [76]. In the case of cancer therapy, nanomaterials have been widely employed because of their unique physiochemical properties, such as passive or active targeting ability, delivering multiple therapeutic agents with the lower side effects compared to conventional chemotherapy [77]. For microbial infections, metallic nanoparticles, particularly silver (Ag) and zinc oxide nanoparticles have showed excellent antimicrobial effects with ability of bypassing multidrug resistance barriers [78, 79].

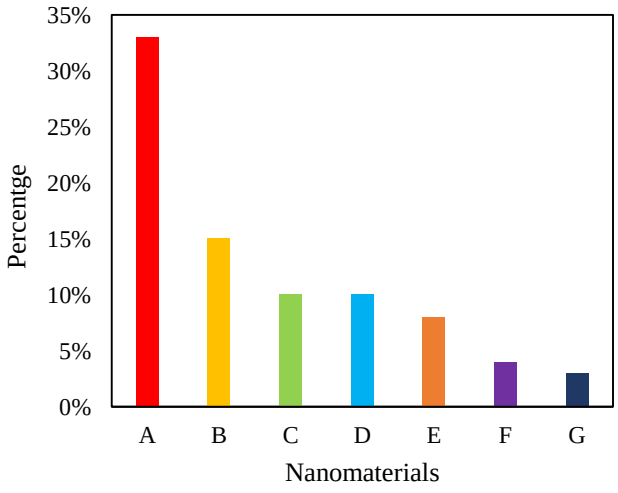

Fig. 2. Important organic and inorganic nanomaterials in various stages of clinical translations or in the market; liposome or lipid-based nanoparticle (A), antibody-drug conjugate (B), polymer-drug/protein conjugate (C), polymer (D), viral vector (E), cell-derived vehicle (F), and inorganic nanoparticle (G) [76].

Conclusions

When conducting research in experimental settings, it is standard practice to look into a variety of medications, experiment with a range of administration methods, and look into a variety of locations throughout the world. Although it is possible to predict certain changes along the route, there will also be others that come about suddenly. Because of this, it is

extremely important to build trial technologies and processes with sufficient wiggle room, so that sponsors can make improvements as they see fit. In contrast to conventional clinical trials, co-clinical projects decrease the disparity available between pre-clinical investigations and clinical trials.

The clinical trials in both medicine and nanomedicine are currently at an intriguing juncture because specialists in the field have finally admitted that their work is challenging and are actively searching for ways to use that complexity to their advantage and eventually improve patient outcomes. This has created an interesting juncture for the clinical trials business. This begins with a thoughtful analysis of the factors that contribute to the complexity of trials and the means of response that provide the best possibility for sponsors, locations, and patients to benefit from timely and cost-effective studies.

Study Highlights

- It is standard practice to look into a variety of medications, experiment with a range of administration methods, and look into a variety of locations throughout the world.
- In contrast to conventional clinical trials, co-clinical projects decrease the disparity available between pre-clinical investigations and clinical trials.
- Cost and time overruns are more likely to occur in clinical projects that are larger and more complicated.
- The clinical trials in both medicine and nanomedicine are currently at an intriguing juncture.

Abbreviations

CDDI: Cortellis drug discovery intelligence
CRO: Contract research organization
CTFG: Clinical trials facilitation and coordination group
CTFG: Clinical trials facilitation and coordination group
EEA: European economic area
EU: European union
FDA: Food and drug administration
HTA: Health technology assessment
IMPs: Investigational medicinal products
NIHR: National institute for health research

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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