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Review Article

Clinical Trials in Oncology: A Comprehensive Review

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Abstract

Clinical trials are essential to the development of anti-cancer drugs and prolonging the survival of cancer patients. Cost of cancer care has increased over the years in the United States. Clinical trials for cancer differ than trials involving other diseases mainly due to the complexity of the disease. Low incidence rates of certain cancer types and rising clinical costs pose additional challenges in successful completion. Oncology trials are faced with practical and ethical concerns including the inefficiencies in trial execution, increasing use of off-label agents, increasing healthcare costs and increasing reliance on less robust trial designs. By elucidating the characteristics and outlining differences of oncology clinical trials from non-oncology clinical trials, we hope to provide a brief overview to our readers about the unique challenges faced during different phases of the drug development of anti-cancer drugs, as well as common features of clinical trials across the spectrum.

Keywords: *Clinical Trials; Oncology*

Abbreviations

NCI: National Cancer Institute; FDA: Food And Drug Administration; CRF: Case Report Forms; CDISC: Clinical Data Interchange Standard Consortium; DMC: Data Monitoring Committee; IRB: Independent Review Board; SOC: Standard Of Care; OS: Overall Survival

Introduction

Cancer is the second leading cause of mortality. According to National Cancer Institute (NCI), there are over 200 different types of cancer, depending upon the organ and disease [1]. Therefore, a significant effort is involved, in terms of financial investment and time, in developing cancer-specific treatment modalities. Multitude of therapeutic approaches are being studied right now in clinical trials by academia, biotech and pharmaceutical industry. The clinical trial is a standardized, controlled, unbiased and objective evaluation of the effectiveness of the cancer treatment. It is the final step where initial development of a new cancer drug culminates. The design of clinical cancer research studies requires a concerted and collaborative efforts between clinicians, scientists and statisticians in the design, execution and analysis of studies. It requires a broad conversation between clinicians and patients to achieve patient's trust and ensuring patient's safety [2].

While in some ways, clinical oncology trials can be similar to non-oncology trials, cancer trials can pose unique challenges for its successful completion. Oncology trials often suffer from low participation rate, inadequate patient enrollment, lack of trust between patient and doctor, and financial constraints. It requires a great amount of effort from clinicians, physicians and researchers who make sure that the trial is being conducted in a scientifically sound manner in every way possible [3]. At the same time, authorities like institutional review board (IRB) ensures and safeguard the patient's rights and safety. They assess the risk/benefit profile of a trial to

make sure that any harm, if there is reasonable to potential benefits of a drug under investigation. To remove bias, additional layer of data safety and monitoring boards (DSMB), are involved to ensure the progress of a clinical trial, to inform investigator of safety issues, patient dropout and futility of the trial [4]. Food and drug administration (FDA) play a vital role in evaluation of therapeutic benefit of a drug after weighing its risk-benefit profile, despite ensuring validity of the data and integrity of the trial. They have added powers vested in them such that they can halt the clinical trial, issue complete response letter (CRL) to the manufacturer and ask the investigator to conduct additional studies [5].

This article encompasses a broad overview of the oncology clinical trials including various types, their design, role of IRB and DSMB as well as challenges faced during cancer clinical trial.

Types of clinical trials

Oncology is different from other therapeutic areas in the sense that not all oncology compounds can be studied in healthy subjects and hence, most studies are conducted in patient populations. These clinical studies can either be interventional or observational. During the interventional trials, patients are treated with a new drug, device, or procedure. The investigational treatment can also be compared with the available competitor or placebo to determine the effectiveness or show superiority of the investigational drug. It advances our understanding of how cancer works [6]. During observational study, subjects are monitored while they are on a pre-determined treatment and no intervention is made in any scenario. Table 1 and table 2 summarizes the different types of clinical trials, depending upon the blinding and desired outcome, respectively.

Double blind randomized trial [7]	Single-blind randomized trial [8]	Open-unblinded trial [9]
• Gold standard • Patients and researchers blinded to cancer treatment	• Volunteers are blinded to the cancer treatment, but researchers are aware.	• Both researchers and patients are un-blinded • E.g. during surgical treatment or studies involving Marijuana.

Table 1: *Summary of different types of oncology clinical trials.*

Case-control studies [10]	Cohort studies [11]	Cross-sectional studies [12]
• Retrospective studies • Cancer-group against control • Lifestyle/genetic differences between two groups are compared	• Prospective studies • Use to find cancer risk factors e.g. will eating meat increase the incidence of cancer?	• Evaluate disease interaction with other factors at a point in time • Difficult to prove that correlation between factors and cancer

Table 2: *Summary of different types of clinical trials which depending upon the outcome desired.*

Before the initiation of human clinical studies, the investigational drug is studied in animals and *in-vitro*. After successful testing, the data is sent to the Food and Drug Administration (FDA) for review and feedback. The FDA reviews the data and provide the appropriate response, guidelines and feedback to start conducting the investigational drug for testing in humans. Once the approval is granted to test the drug in humans, the clinical trials are usually conducted in four phases (phase I-IV). Each phase is a separate clinical trial, and the data should be submitted to the FDA on rolling basis or at the end of each phase. Once the FDA completes its review for a particular phase, it notifies the investigator of its decision to start the next phase of the clinical trial and whether or not any additional works needs to be accomplished to address any concerns [13].

Different phases of clinical trials

Phase I study

Phase I trials are conducted to find out more about safety and dosing in a small set of volunteers. Usually this type of studies will have 20 - 80 participants. Even after the preclinical research, where safety is evaluated in animals, it is not uncommon to see unwanted side-effects of a drug during the Phase I trial [14]. Table 3 summarizes the differences in oncology and non-oncology phase I trials.

Phase I Non-Oncology Studies	Phase I Oncology Studies	Reference
Conducted in healthy volunteers	Conducted in targeted population	[14]
Evaluated for maximum tolerated dose	Evaluated for recommended phase-2 dose	
Comparatively easy to recruit patients	Studies are in general more costly and patients are difficult to recruit	
Relatively shorter recruitment period	Longer recruitment period	

Table 3: *Difference between oncology and non-oncology phase I trial.*

Phase II study

These trials test the efficacy of the drug in single or multiple ascending dose. This phase can consist of 100 - 300 participants. It further evaluates the safety of the drug in a larger population. Investigational drug can last 1 - 2 years in this phase of the development [15].

Phase III study

Phase III studies involve randomized and blinded trial in couple of hundred to several thousand human subjects with targeted disease. These are usually very large studies, being conducted multiple sites and in multiple continents. Phase III trials can last from 2 - 8 years depending upon the kind of primary endpoint, disease progression, and type of cancer. Due to the larger number of participants and longer duration or phase III, rare and long-term side effects are more likely to show up during this phase. After positive phase III trials, the pharmaceutical company can request the FDA approval for marketing the drug. This review can take up to 10 months. However, for certain indications and rare diseases, priority review is usually granted to fast-track the approval of drug in 5 - 7 months after the submission of investigational new drug application (IND). If investigators demonstrate that the investigational drug is safer and more effective compared to the competitors on the market, the FDA will usually approve the drug. During the post-approval marketing surveillance, investigators monitor participants for several months or years to see how effective the medication is and to gather more information about any side effects it might cause during its user in much larger and broad population [16].

Phase IV study

This is often done when the drug is already available on the market. During this phase of the study, the drug could be compared to other drugs already in the market, monitor the effectiveness, or could result in a drug taking off the market due to severe side effects [17].

Challenges in oncology clinical trials

Recruitment of patients in clinical trials

As mentioned earlier, there can be more than 200 types of cancer. It is not a single disease like diabetes or hypertension. Hence, cancer diverges into different subtypes depending upon the affected organ e.g. pancreatic cancer, lung cancer, bone cancer, or within an organ-specific cancer, it can be further classified into type of mutation involved. In oncology trials, it is generally difficult to have patients recruited for the clinical trials intended to treat specific cancers. In the Unites States, only 1 out of 20 patients give consent for participation in the oncology clinical trials. There are various reasons for low rates of participation. Health of a cancer patient is usually

in a very deteriorated state which impedes the successful participation throughout the lengthy trial. Even if they are willing, and consent to enroll in a trial, according to a study, for 47% of the cancer patients, no trial is available [18]. Design of a clinical trial usually involves a very narrow inclusion or exclusion criteria. Therefore, even if a patient is available, study inclusion/exclusion criteria might make them ineligible to enroll for the treatment under investigation [19]. Moreover, physicians form a close relationship with patients, and their opinion regarding a specific investigative treatment affects the decision of the patient to enroll in a trial [20]. One reason is that, subjects don't trust the treatment or doubt the significance of the clinical trials due to the fear of randomization, past infamous drug development fiascos etc. Sometimes, it is hard to recruit patients for a specific cancer type due to their low incidence rate e.g. recruitment for an investigational drug to treat gall bladder cancer can be very difficult, since the patients having this specific type of cancer are limited [21]. This challenge is usually overcome by recruiting patients in different countries and continents across multiple clinical sites. During a clinical study, some patients also drop out, requiring replacement of these patients, which can significantly delay the anticipated completion time of the clinical trial in addition to increase the already expensive trial. To summarize, multiple factors can affect an oncology clinical trial completion in a significant way and this often poses significant challenge for investigators, thus differentiating oncology and non-oncology trials [22].

Inefficient trial design

Too many dropouts during the trial progress can not only add more burden to investigators to enroll substituted patients, and increase the cost of the trial, but it can render the study statistically under-power or there can be some endpoints where sample size is not enough to investigate the success or futility of the trial [23]. Due to the difficulty in recruitment of subjects, a clinical study may end up having a trial design which is sub-optimal. Design of single arm study for a phase II trial in order to speed up drug development timeline and reduce the associated costs, can confound the effectiveness of the investigational drug. Failure to enroll positive control arm, will eventually hinder the ability to show superiority of investigational drug compared to the positive control or competitor. Patients should be randomized for control and treatment arms and trials should be blinded whenever possible. Lack of randomization will introduce bias in the results [24].

Data collection and interpretation

Selection of inefficient trial design impacts the next step i.e. data collection and interpretation. Data are unarguably the ultimate measure of clinical trial performance. Appropriate trial design, well-thought-out case report forms (CRF) and clear CRF completion instructions are among the first steps to ensure that the data is being consistently collected in order to achieve the trial objectives. This is all inter-related, starting from the recruitment of patients to the collection of the data. Monitoring visits are one of the most resource-intensive activities to ensure valid data is collected [25]. FDA has provided guidance on an integrated approach to monitor clinical trial quality and subject safety through a risk-based centralized monitoring approach. These efforts are augmented by ongoing data cleaning and monitoring to ensure data accuracy [26]. The main idea is to implement a central, systematic, and ongoing review of data which allows the monitoring to be more focused and data-driven. Continued advances in technology, data sharing standards including Clinical Data Interchange Standards Consortium (CDISC), and the increasing sophistication of data visualization tools promise to increase efficiency and reduce the clinical trial cost [27].

Complexity in maintaining and monitoring safety

Patients dealing with cancer can have multiple diseases and therefore, they are usually administered multiple treatments. In this scenario, it becomes complex to maintain and monitor the safety of the patients due to the drug-drug interactions and physiological interactions between diseases e.g. a diabetic patient having kidney cancer, may be taking a higher dose to regulate blood sugar level which may impact the growth of kidney cancer cells during the clinical study, ultimately compromising the efficacy of investigational treatment for kidney cancer [28]. Hence, these patients should be monitored carefully, and every effort should be made to minimize any expected

interactions with the other diseases or drugs. In addition, medical records should be maintained carefully. Usually, a data monitoring committee (DMC) is mandatory to ensure the safety of the trial subjects and to maintain the integrity and validity of the trial itself [29].

Economic constraints on the conduct of trials

The cost of conducting clinical trials starts from the recruitment procedure to the approval of a drug by the FDA. It is a strong barrier to conduct clinical trials, which is driven primarily by the time and resources required to activate trials and reach accrual targets [30]. The need of the financial resources for carrying out the clinical study may vary due to variety of reasons e.g. costs vary due to the number of patients enrolled at a site, complexity of the condition being studied, the requirements of the aforementioned clinical trial protocol, and the phase of the clinical trial. Basically, the cost involved in the entire clinical study can be sub divided into different areas [31]:

- Investigator and site: Institutional overhead, investigator honoraria and fees, ethics review, Institutional Review Board (IRB), investigator meetings and associated travel costs.
- Patient enrollment: Recruitment costs (advertising, travel stipend, etc.), screening, office visits (equipment, diagnostics etc.), study visits.
- General trial procedures: Initial exam, physical exam, vital signs, detailed medical history.
- Materials: Drug supply, comparator drug, other equipment, shipping, etc.
- Efficacy assessments: MRIs, CT scans, other diagnostic tests etc.
- Laboratory: Local lab fees, storage, shipping of samples, etc.
- Site-based IT/data management: Trial master file, electronic data capture, interactive voice/web response system.
- Site-specific contract research organization (CRO) related expenses: Monitoring, randomization, biostatistics, travel, meetings, etc.

The clinical trials can take almost 10 - 15 years to develop a drug for the use of patients. Cancer patients usually have very little time left in their life to see the whole course of the drug development. Therefore, time management matters a lot. Many patients might be in the advanced stages of cancer, and they usually have high hope from an investigational drug to prolong their survival. Due to the time restrictions associated with cancer progress, regulatory authorities around the world have become a little liberal for approving a drug and its use in the target patient population, even if that drug carries some side effects or it can only increase overall survival by couple of months [32]. Although FDA keeps an eye over the safety and efficacy profile of a drug to ensure the patient safety, criteria to meet primary endpoints are usually more relaxed in order for a drug to be used by the cancer patients in their advanced stages to prolong their survival [33,34]. For example, if a drug is tested on individuals having a tumor, and it is noticed that after three weeks the size of the tumor is reduced, and the time of the patient's life is increased to some extent then FDA approves that drug [34,35] However, faster review times may result in inadequate time required for gathering more safety data and higher prevalence of post-marketing label changes can been seen in such cases, as more safety and efficacy data regarding the use of a drug emerges.

How phase III oncology clinical trials are conducted?

Phase III oncology trial is the most extensive part of the drug development. It decides the fate of the drug by comparing its effectiveness in targeted patients against a standard drug available in the market. It tests the safety and efficacy of a new anti-cancer drug that has shown promising safety and efficacy trends in Phase II trials in relatively small patient cohort. In a Phase III trial, the study drug is tested in a large number of patients with statistical rigor. Each Phase III trial has strict and well-defined eligibility criteria (i.e. inclusion and exclusion criteria), and those monitoring trial enrollment must ensure that the patients enrolled in the trial meet these criteria [2]. Phase III oncology trials are typically double-blinded and randomized trials. Stratification techniques may be used to ensure a balanced distribution of specific important patient baseline characteristics among the treatment arms to control confounding factors [36].

In the two-arm parallel study design, patients are randomized to either the study drug or the standard of care (SOC). This design is most commonly used for Phase III oncology trials. Patients on trial are allowed for ethical reasons to take subsequent anti-cancer therapies at the end of the trial. However, subsequent therapies taken by patients in both treatment arms after discontinuation of trial therapy confound and bias the estimation of overall survival (OS), which is the FDA's gold standard for clinical benefit. In recent past, several publications have shown that short term clinical end points such as response rates can be used as surrogate for long term survival-based end points to accelerate drug approval by the agencies and availability of new drugs to the patients [37].

Phase III oncology trials are commonly superiority trials (i.e. to test if the study drug is superior to the SOC in terms of the primary efficacy endpoint and not worse in terms of safety). However, these trials may also be designed as equivalence trials to test if the study drug and the SOC have similar efficacy within an equivalence margin, or non-inferiority trials to test if the study drug is not worse than the SOC within a margin [38]. Non-inferiority trial designs are commonly used in biosimilar trials/studies - to investigate whether a biotherapeutic product is similar in safety, efficacy and purity to an existing one [39]. During phase III, either one statistical analysis may be performed at the end of the trial or several pre-planned interim analyses, known as a group sequential design, may be performed. In a group sequential design, the following are pre-specified for operational ease: total number of looks planned and a stopping criterion to reject, accept, or either reject or accept the null hypothesis at each look i.e. one can stop the trial at each look for efficacy alone, futility alone or both, efficacy and futility [40]. Another class of designs gaining popularity is adaptive designs. In an adaptive design, one can analyze the interim/accumulating data and modify certain features of the study design midway through the trail. However, the validity and integrity of the trial needs to be ensured by pre-specifying in the protocol all the adaptations that are intended to be performed in the interim. One example of an adaptive design is increasing the sample size while preserving the overall type I error rate when the interim data suggests that the observed conditional power is low. Bayesian techniques, which assume prior probability distributions and update these using the interim data to yield posterior and predictive distributions, may be used in adaptive designs. Bayesian techniques are statistical tools that can be used in either the adaptive or classical trial design setting, just as frequentist techniques can be [41]. Statistical analyses for a Phase III trial tend to be extensive and can commonly include more detailed analyses such as competing risk analyses; for example, in a breast cancer trial, discontinuation from treatment due to an adverse event is a competing risk for progression free survival, a possible efficacy endpoint in such a trial [2].

IRB review and approval in oncology clinical trials

Before the clinical trial starts, the ethical board called IRB will review the study. An IRB is made up of doctors, researchers, and other members. Its role is to make sure that participants are protected, patient's rights are safeguarded, and safety protocols are being followed. Their role is to make sure that research risks are minimized and are reasonable in relation to any potential benefits. The IRB also reviews written informed consents involved in the research. They continue reviewing the trial once or twice the year. Members of IRB will review the data and provide the advice as per the needs arise e.g. enrollment of more patients due to patient drop-out, carry out futility study to minimize the cost when drug seems to not meet its primary endpoint, monitor safety of the patients etc [4].

As usual, development of treatment modalities for cancer faces some challenges which are unique to this area. FDA regulations states that the IRB groups are designated to review and monitor the clinical trial research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications or disapprove research [42]. This group plays a very important role in the protection of the patients and human rights. The purpose is to make sure that the pharmaceutical companies take appropriate steps to protect rights and welfare of participants. IRB will review all study related materials according to FDA regulations. During Phase III review process, the IRB will pay close attention to the structure of the trial, ICF process and form, blinding plan (if applicable), conflict of interests, principal investigator's qualifications etc [43]. What design or structure of trial is appropriate and how it may affect the rights and safety of patients, is regulated by the IRB. Without its approval, a trial can not commence. In oncology clinical trial, it is difficult to convince patients to take a new treatment that has not proven efficacy yet, and general toxicity of anti-cancer drugs augment a patient's

apprehensiveness about the enrollment in the trial. Once they agree to participate, nothing takes precedence over the safety of the patient, to maintain the good faith in the eyes of the public. Any nuisance created during a clinical trial, can amplify the public mistrust in drug companies. The job of the IRB is to make sure that the research is ethically sound and to suggest ways to improve it [44].

Informed consent is one of the most important ethical dimensions of research on human subjects, and yet it is debatably the most difficult to truly achieve. Fully informed consent has three fundamental components: i) Adequate disclosure of all the pertinent information regarding a drug and the trial; ii) Full patient capacity to comprehend the information provided at the beginning of the trial; and iii) Freedom of the patient to make a decision. A patient is entirely unable to know in advance whether participation in a study might be of personal benefit. The clinical investigator must be completely honest about presenting the experimental nature of the treatment being offered and must avoid propagating the widespread therapeutic misconception [45]. IRB should monitor that the patients are given adequate yet comprehensive information in an easy way for them to make an informed decision about enrollment in a particular trial. The ICF is a part of the informed consent process, designed to complement, not replace, a discussion between researchers and subjects, and to serve primarily as documentation rather than an educational tool. At no step, patients should be misled about the potential of the cancer drug, and nature of the study. Toxic side effects and their severity should be clearly communicated to a cancer patient in order for them to understand the severity of a treatment in its full effect. Studies suggest that in-person discussions should focus on the aspects of consent form which are most often poorly conveyed through the ICF—specifically the experimental nature of treatment, associated risks, and benefits. Patients should be notified of alternative treatment available if it can increase their OS more than the investigational drug for which patient is being enrolled [46]. These knowledge domains may be best suited for face-to-face discussions with expert clinicians, who are easily adaptable to patient's level of education, cultural characteristics, and can include an interpreter for patients not proficient in the national language of the country where those trials are being conducted. Such conversations are known to omit some components of the informed consent, and their completeness and linguistic complexity varies considerably among clinicians, so other critical knowledge domains may be delegated to an ICF review with non-clinical research staff. To improve the patient understanding, the role of clinicians and non-clinical staff should be clear [47].

Oncology clinical trials are very complicated studies and highly regulated. They usually include several steps with numerous decisions and intensive review processes at various levels. In the 1970s, concern about the inadequate protection of human subjects in research led to federal regulations and the establishment of IRBs. During that time, most clinical research was done at single sites by single investigators. Since then, the increasing emphasis on evidence-based clinical practice has greatly increased the number of clinical trials. There has also been substantial growth in the number of multicenter oncology trials as well as an increase in their complexity. In addition, the purview of IRBs has been expanded as additional regulations regarding human subject's research have been developed, such as the "Privacy Rule" promulgated under the provisions of the Health Insurance Portability and Accountability Act (HIPAA). Downside is that these combined changes have overburdened IRBs and have fostered long delays in the review of study protocols and ICFs [48].

In many cases, the oncology trial sites will have their own IRB. The board will include at least one expert in the therapeutic area who can help with the protocol and ICF review. There are many other members who will play a significant role in the study approval process. Cancer is a deadly disease which affects 1.5 million people affecting every year. These trials can become very aggressive to find the potential cure as financial gains are very lucrative. These clinical trials bring benefits but also risks. The role of the IRB is to weight the risks and benefits in order to help researchers and patients fight the disease. E.g. NCI has a dedicated review board who will review the protocols with a scientific interest, focusing on originality, methodology, feasibility, and relevance [49]. This is a requirement for the oncology studies. Most of the clinical research studies proceed directly to the IRB. However, the cancer trials will go under institutional scientific review first. This procedure is a good insurance, or some can say another set of eyes. All government sponsored research must follow this review. Many pharmaceuticals companies seek the scientific advice before presenting the protocol to other authorities. Sometimes, the FDA will ask for the pivotal trial with small group of people. The data after this stage will be submitted to the FDA for

analysis. After the scientific review, the study documents will be submitted to the IRB. The IRB won't just review the study but will also review the progress of the ongoing trial at least once a year. The board will include at least five people and must have: one scientist, one layman, one person who is not associated with the institution where the trial is taking place and who is not an immediate family member of someone who is associated with that institution. The board also can have doctors, patient advocates, social workers and others [50]. All clinical research studies follow three principles outlined in the Belmont Report and oncology trials are no exception.

Conclusion

In conclusion, there are lots of cancer clinical investigations which are being conducted every year. Oncology studies are complex, expensive and time-consuming. Every single trial will face challenges like subject enrollment, vendor management, funds, and many other things, but oncology trails are different due to the inherent nature of the disease progression and huge patient sentiment. Investigators need to be aware of the challenges in terms of patient enrollment, rising clinical costs and enhanced scrutiny by IRB. The role of the IRB in the modern clinical trials is crucial to maintain the integrity of the research.

Conflict of Interest

The author declares no conflict of interest.

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