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Clinical Research: An Overview of Study Types, Designs, and Their Implications in the Public Health Perspective

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Abstract Human health is plagued by several challenges throughout life. Different endogenous and exogenous factors influence the well-being of humans. The endogenous factors may be the enzymes and hormonal functions that alter the normal human physiological status and cause diseases like metabolic disorders, organ dysfunctions (liver diseases, heart diseases), and several others. Also, the human immune system and the cells involved in the immune responses may be disturbed causing autoimmune disorders, and tumors/cancers/malignancies. The exogenous reasons for human illnesses may be infectious diseases caused by microbes, chemicals, toxins, and others to those humans get exposed during their lifetime. The management of such illnesses and diseases is generally carried out by qualified physicians, and surgeons, and respective clinical experts in healthcare institutions that include hospitals. The drugs, devices, and other agents used to manage human diseases are synthesized and tested exhaustively before being approved and marketed for human use for their safety and efficacy by performing clinical research. In this review, we attempt to delineate the different types of clinical research and their implications.

Keywords: *human health, endogenous, exogenous, immune system, clinical experts, clinical research, drugs, hospitals, healthcare, safety, and efficacy*

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1. Introduction

Research is a systematic approach to solve a problem. Research studies are broadly divided into primary and secondary research types. The primary research includes observational research and experimental research. The observational research is composed of descriptive studies like case studies, cross-sectional studies, surveillance, and ecological correlational studies. The experimental research involves an intervention that generally is a novel drug. People involved in clinical research include the sponsor, the principal investigator, the clinical research associate, and the clinical research coordinators, among others.

To be able to conduct clinical research, we require adequate knowledge of the functioning and other important elements of clinical research. Clinical research can be initiated by identifying the problem element, which could be finding a newer drug for treating an old disease/infection or a new disease.

The sponsors, the principal, and co-investigators in combination with the clinical research associates, clinical research coordinators, and the institutional heads where the clinical research is being conducted, all work in coordination for a successful clinical trial. It is important to regularly review the procedures, safety of the study participants, the merits, and the demerits of clinical research before initiating and thereafter in regular intervals [1].

Informed consent of the study participants is of great significance in clinical research. The study participants should be thoroughly informed about the study protocols, safety, and other trial-related information. In a previous study, it was observed that the subjects involved in a cancer research clinical trial were not completely aware of the essential elements of the trial, which may limit the success of the research [2].

The regulatory bodies like the US food and drug administration (FDA), and the central drugs standard organization (CDSCO) in India are instrumental in regulating drug development and marketing, which includes the implementation of good clinical practice guidelines (GCP).

To be able to conduct clinical research successfully, one should be well versed with the elements of clinical research and the functionalities of each element. Since most clinical research studies concentrate on developing and assessing the performance/activities (benefit/adverse events) of newer drugs/pharmaceutical agents, and because human subjects are used during the research, those conducting clinical research must be having adequate knowledge of the consequences.

A recent research report from India assessed the adequacy of knowledge among the medical and dental

postgraduates regarding the ethics and the adverse drug reactions during the conduction of clinical research [3]. The results of this research noted that the knowledge of clinical research was similar among the medical and dental postgraduates (p=0.351). Very few postgraduates (13%) knew about the database on reporting the adverse drug reactions, and most (66.5%) knew about the adverse drug reactions. There was adequate knowledge of the ethical issues in clinical research (44%) followed by the knowledge on the concepts of unethical experiments (49%).

Because among all the elements of clinical research the ethical concerns assume increased significance, the researchers involved in clinical research should be well versed with the ethics as emphasized by previous research [4].

In this review, we attempt to comprehensively describe the essential elements, different types of studies, and the implications of study designs on clinical research.

2. Review

2.1. Recruiting the Study Subjects for a Clinical Research

Among various hurdles in clinical research, recruiting an appropriate number of study participants assumes great significance. The hypothesis (null and alternate hypothesis) or an assumption forms the basis of clinical research. Because the results of clinical research reflect on the total population, selection of study participants assume importance. There are different types of sampling techniques (Probability/Random and non-probability sampling) and errors in clinical research (bias and confounding).

Among the factors that influence the success of a clinical research/trial, the subjects/samples involved in clinical research are considered the most significant elements of clinical research. The greatest challenge in the conduction of clinical research probably arises during the recruitment of the study participants.

Previous research had elaborated the two important principles of sampling that include adequacy, and appropriateness. This paper delineates the measures to calculate the number of study subjects to be included and the appropriate inclusion and exclusion criteria among the study subjects included in the study [5].

Sampling may be influenced by ethical issues, finances, infrastructure, time, and other miscellaneous factors [6]. Another study emphasizes the significance of calculating the sample size to be able to conduct a fruitful clinical trial/research, wherein a new drug may get approval for human use [7].

Reviewing and approving the clinical trial protocols, regular auditing of the research and researchers' progress, and the most important of all, the confidentiality, rights, and safety of the study participants are key to success in clinical research. A significant hurdle in clinical research is the sampling bias, also other types of biases that may influence the results of the clinical research [8].

Previous research had reported the perception and attitudes regarding clinical research participation among the general population in Qatar [9]. It was observed that only 5.7% of the population was approached with a request to participate in clinical research. Of those approached, more than 60% agreed to be a part of clinical research. Of interest in this study was the disinterest among the participants was mostly due to time constraints (47.5%), and the other reason was fear (11%).

In another qualitative study from China which assessed the factors responsible for the conduction of quality clinical research, it was noted that the lack of infrastructure, other resources, and deficient human research protection policies may hamper the clinical research results and its quality [10].

Clinical research in the areas of rare genetic disorders and those involving the pediatric population have been noted to suffer from several factors that also include recruitment of study participants [11,12].

Given the variable perception of research subjects with regards to their participation in clinical research, the clinical research management must carefully consider safety over the outcome and ensure all ethical aspects are fully satisfied while recruiting study subjects and until the completion of the research.

2.2. Study Designs in a Clinical Research

Probably, preparing a study design, plan, or protocol is the most significant aspect of clinical research. The main types of clinical research are qualitative research, quantitative research, the mixed methods research, prospective and retrospective research. Qualitative research includes interviews and observations whereas observational and experimental research constitute quantitative research.

To perform reliable, and reproducible clinical research, research design must be planned appropriately. Only the results obtained from clinical research conducted according to a well-defined and appropriate design can produce reliable and reproducible data.

The choice of a study design depends on the problem of research, subjects available, financial limitations, and duration/time constraints. The study designs most used in clinical research include observational and experimental studies. Among the observational studies, case studies, cross-sectional studies, and cohort studies are frequently done. Of the experimental studies/interventional studies, the correlational studies, randomized, and non-randomized studies are frequent [13].

The other most frequently done research type is the cross-sectional study. Here, the recruited study subjects are interviewed or asked to fill in the questionnaire. The utility of such type of research greatly depends on the quality of the questionnaire prepared and the attitude of the responder, as well as the mode of extracting the data (mobile, e-mails, interview in person, etc.).

Traditionally the design of a clinical research/trial mostly includes three important steps. The selection of a design, followed by the conduction of the research, and finally the analysis of the results.

A recent study had analyzed the application of an adaptive study design, where at the phase of conduction of research, the researchers may review and adapt a small modification (unplanned during the design of the study)

[14]. The implementation of the adaptive study designs was noted to speed up, shorten, and improve the clinical trial outcomes.

Analysis of a bottom-up pathway and its implementation in the context of intensive care units has recently been evaluated in a study from Sweden. This report had suggested that there is a need for increased inter-professional collaboration for the success of such models [15].

2.3. Implications of Descriptive Type of Clinical Research

It is important to know which type of research study/design is useful to draw conclusions from clinical research. The descriptive type of clinical research includes correlational, cohort, cross-sectional, and case studies [16]. Among these, the case studies and case series may benefit the understanding of a new disease/clinical entity. Descriptive studies are also used to understand the potential risk factors of a disease/condition [17]. These studies are generally undertaken to take health-related, and patient management decisions.

Descriptive clinical research is among the most frequently and easily conducted studies. The descriptive studies investigate research questions like “what is it”, “where is it seen”, “when is it seen”, and “in whom is it observed”. They can be observational (case study, correlational, case series, cross-sectional) or interventional/analytical (cross-sectional, case-control, and cohort) in nature.

These methods can be used to study individual cases and population-based studies and they apply simple statistical methods (mean, frequency, etc.) to derive research results. The drawback of a true descriptive study is that they lack a control group/comparison group and the results drawn from such studies do not necessarily reflect the population.

These are probably the most feasible type of clinical research, especially in economically weak third-world countries. Descriptive studies can be quantitative or qualitative in nature. Here, the study participants are provided with a structured questionnaire. There are several other methods to obtain the data in a descriptive study that include interviews, e-mails, telephonic conversations, and others.

The results of an appropriately conducted descriptive clinical research may be used to make policy decisions by the respective governments on public health-related issues.

In this type of clinical research, we can find out the factors, and the perceptions of the participants regarding an aspect. A study previously had tried to identify the perceptions of the participants and the factors that may influence the participation in clinical research being conducted for research to find a cure for HIV disease [18].

The peoples' perception of participating in clinical research can be assessed using descriptive qualitative studies as noted from a recent research report from Korea [19]. This research noted that the Indians were more than willing to participate in clinical research as compared to their Korean counterparts (58.9% vs. 39.3%, $P < 0.001$). These findings may point to the fact that people from developing and poor countries could be willing to participate in clinical research for financial benefits as compared to the developed nations.

2.4. Analytical Research Using a Case-Control Model in Clinical Research

Among the clinical research designs, we have observational studies and experimental studies. Of the observational studies, there are two types, the non-inferential studies, and the inferential studies/analytical studies.

The most essential elements of analytical clinical research studies are exposure and outcome, cause and effect, risk factors of the disease, the independent and dependent variables.

Case-control studies are among the most frequently performed clinical research studies. These studies identify two study groups, one the case group, and the other is called the control group. The case group includes the diseased (outcome) population, and the control group is those who do not have the condition.

Such research design is also used to understand the link between the risk/predisposing factors (exposures) and the outcome/disease. The most significant aspect/element of the case-control studies is the recruitment of appropriate study participants.

The researchers should understand that a bias in the selection of the study participants may influence the results of the clinical research. To reduce/minimize the errors, the cases, and the control group should be matched in age, and other factors.

Case-control type studies are generally suitable to research rare diseases and are cost-effective. They cannot be used to study populations with risk factors and multiple diseases [20].

A recent study was done to assess the relationship between the gene-environment from an ovarian cancer perspective [21]. The application of the case-control model in colorectal cancer has been recently reported. This research tried to find the relationship between smoking, age, and sex and the risk of developing colorectal cancer [22].

2.5. Implications of Observational and Cross-sectional Studies in Clinical Research

Among the observational studies, cohort studies are routinely used to perform clinical research. The types of cohort studies include prospective, retrospective, and Ambi-directional studies. There are different designs, and steps involved in cross-sectional studies and their applications in clinical research as compared to cohort study designs.

The observational studies are appropriate to study designs (case-control, cross-sectional, and cohort) while choosing to research the etiology of a condition/disease, and while studying a rare condition. Cross-sectional studies are a type of observational study that can either be descriptive or analytical/inferential studies. These studies are used to identify the risk factors and other influential variables in the development of a disease/condition. The

advantages of the cross-sectional studies include their cost-effective nature and require less time. The drawback of cross-sectional studies includes their unsuitability to be used in rare diseases/conditions. Case-control studies are usually plagued by bias and confounding factors.

Among the observational studies, only cohort studies are used to identify the predictors (exposure) of disease (outcome) [23]. But the cohort studies are not cost-effective (prospective) and retrospective cohort studies may be plagued by bias.

Observational research designs fall into the category of primary research. Such research concentrates on just observing the relationship between the factors influencing the outcome [24].

A recent research study from Spain had attempted to compare the utility of cohort and cross-sectional studies to identify the adverse reactions/events in a clinical trial. This study had noted that the cross-sectional studies may not be more superior to the cohort studies in identifying the adverse events [25].

It was confirmed in a recent study that under appropriate conditions that include the exposure (time of exposure), and correct interpretation of the results, we assess the prevalence of a disease and its burden by using cross-sectional studies [26].

The cross-sectional studies of a prospective type can also be used to analyze multiple factors for their influence in the development of an effect. A recent study had prospectively studied the relationship between sleep, screen time, school travel, and sport participation with moderate to vigorous physical activity [27].

2.6. Experimental Study Design in a Clinical Research

Of all the available methods of conducting clinical research, the experimental study designs have been noted as the most significant ones in drawing accurate and reliable results. With a historical background associated with the experimental designs (pre-experimental, true, and quasi-experimental designs), they were routinely and successfully used in clinical research to precisely identify the factors (both internal and external factors) influencing the disease and the effect of the drug, thereby minimizing the confounding elements/factors. There are several elements involved in controlled, uncontrolled, and randomized experimental clinical trials.

The experimental study designs are also called interventional study designs. In this type of clinical research, the new/novel drug is tested for its efficacy and potential toxicity. It can be randomized, or non-randomized, and controlled or uncontrolled.

There are several advantages of experimental/interventional research. It is easy to control the variables (dependent and independent variables), the results can be duplicated, can determine with accuracy, the cause (exposure) and the effect (outcome), and this type of research can demonstrate any relationship within the variables [28].

The major drawback of experimental/interventional clinical research is the probability of the new manufacturing drug causing serious/adverse side effects/toxicity. It, therefore, suffers from negative propaganda and stagnation due to regulatory processes as noted from Indian research [29]. Also, this type of research may be plagued with ethical concerns and financially demanding.

A recent study had evaluated the efficacy of experimental study designs in in-vitro fertilization (IVF), an example of the most naturalistic experimental design [30].

The randomized clinical trial type of experimental design is effectively used to understand rare diseases. This research confirms that by improving the research infrastructure and avoiding waste in clinical research we can make the experimental study design a success [31].

The experimental study designs can be factorial where an experimental study design is planned by optimizing the multi-component interventions that include type of intervention, method of delivery, and implementation strategies [32].

2.7. Clinical Research Evaluation by Systematic Reviews and Meta-Analysis

Because clinical research is mostly performed for the development of a newer drug for a disease/condition which does not have a treatment or to develop a drug with more/improved efficiency, and since clinical research is time-consuming and financially demanding, researchers perform an evaluation of the available research results, which is called a systematic review and meta-analysis.

Evaluating the results of clinical research, and their significance in real-life scenarios assumes increased importance. The systematic reviews and meta-analyses can be performed using the journal indexing databases to find and analyze the clinical research studies. The characteristics of systematic reviews, and their essential elements include the literature search, data collection, inclusion/exclusion criteria.

The differences between the routine literature reviews (non-systematic reviews) and the systematic reviews are that the latter comprehensively evaluates the outcomes of various clinical trials/research studies and proposes recommendations that necessarily benefit patient management. Other study designs like the adaptive study designs and meta-analyses could be used to assess the efficacy, advantages, and disadvantages of clinical research in a defined problem area.

Systematic reviews and meta-analyses are a type of study which collects, analyzes, and presents a newer perspective of already published data. These studies usually analyze the clinical research studies to conclude if a particular drug is efficient, and with minimal side effects, and if it can be used in daily clinical practice.

Such studies are easy to perform but are done with utmost care to remove any bias either from the selection (inclusion) of the studies included or any other bias of exclusion.

Also, systematic reviews and meta-analyses can be done to evaluate the efficacy of various available diagnostic tests as evidenced from the results of previous research [33].

The drawback of systematic reviews may be that the studies with methodological quality can be included, and the outcome of such reviews does not necessarily reflect the clinical context as noted from a previous study [34].

A previous study had noted that the results developed from systematic reviews and meta-analyses must be cautiously evaluated due to incomplete reporting, and therefore hinder physicians' practice and decision-makers initiatives [35].

A previous research study had noted that there can be a poor outcome from a systematic review if the stakeholders are involved [36]. Meta-analyses also are done to systematically review the available studies and to conclusively confirm the association (benefit/harm).

A recent meta-analysis had systematically reviewed various studies regarding the available therapeutic options in hepatocellular carcinoma. The meta-analysis in this study revealed the survival rates, disease-free survival rates, progressive-free survival, and safety of the therapeutic intervention [37].

2.8. Statistical Methods to Evaluate the Diagnostic Efficacy

The application of statistics like descriptive and inferential statistics to analyze the collected data will reflect the validity, strength, and reliability of the research outcomes.

Diagnosis of diseases/infections requires various laboratory diagnostic tests. There are different types of diagnostic tests like the gold standard diagnostic tests, the diagnostic tests used for screening populations, and the tests used for the confirmation of diseases/infections. The diagnostic tests and their performances are evaluated based on some important statistical parameters that include the sensitivity, the specificity, and the predictive values like the positive predictive value (PPV), and the negative predictive values (NPV).

Disease diagnosis involves both clinical and laboratory diagnosis. Due to the availability of several diagnostic methods, the selection of an appropriate diagnostic test assumes increased significance. Therefore, the selection of an appropriate diagnostic test is important. The test used to screen should have more sensitivity and PPV, and those used for diagnostic confirmation must be having maximum specificity, thereby helping to rule out the disease (NPV).

Gold standard tests have maximum sensitivity (PPV) and specificity (NPV). The logic here is that no positive should be missed, and no negative should be wrongly reported.

Some diagnostic tests are to detect probable disease in asymptomatic people (screening), some are to assess the treatment prognosis (prognostic), few are for assessing intervention (monitoring), others are for confirming the diagnosis (gold standard) [38].

Diagnostic tests are frequently performed to know if a person has a disease or a condition. The diagnostic tests can be those which are used to test the presence of the disease in people without any symptoms. These diagnostic tests are done in the general population and are called screening tests.

Other diagnostic tests are performed in people who are clinically suspected by the physician to have the disease. These tests must be able to confirm/rule out the disease and are called gold standard diagnostic tests.

A recent study had emphasized the need for researchers and policymakers to understand the intricacies of these parameters and accordingly use various diagnostic tests [39,40].

2.9. Statistical Applications and Risks Associated with Clinical Research

The most important stage of clinical research is the step at which we reflect the results on the general population. Several statistical applications are used to assess the disease prevalence and the incidence of a disease. They include likelihood ratio, odds ratio, hazard ratio, and median ratio. The risks associated with clinical research are not uncommon. Therefore, parameters like absolute, attributable, and relative risk are frequently applied to assess the risk in clinical research.

In medicine, we require evidence i.e., the benefits of a drug, proof that the exposure causes the outcome, and the benefit to harm ratio. Since most clinical research trials/studies involve many subjects, it is important to find the efficacy of a research study using statistics.

To be able to imply the clinical research results on a large population, just by performing the trials on a small representative group requires statistical analysis of the data obtained from clinical research/trial [41].

To understand the results of clinical research and to be able to interpret their efficacy and usefulness in the patient care perspective, applying appropriate statistics is inevitable as evidenced from a previous research result [42]. Although statistical inferences help in assessing the applicability of clinical research in real-world situations, they can also be used to misinterpret/ falsely project the usefulness of clinical research data for financial benefits [43].

A recent study had elaborated on the statistical analysis plans (SAP's) while conducting and interpreting clinical research/trials [44]. The same research also identified the utility of a set of guidelines and recommendations to analyze the clinical research results by avoiding any potential bias during performing and reporting of the results was reported in a previous research report.

If conducting clinical research is one big challenge, applying the statistics on the data obtained from the studies is another great challenge.

The data obtained from the analysis of human subjects about the drug utilization, incidence/prevalence, natural history, and the risk factors of the disease are potentially used to formulate guidelines for taking clinical/treatment decisions among the patients in general as observed by a previous study [45].

A report published previously had observed the possible ways as to how the researchers framed their case report form. This research collected the data using the qualitative interviews of the researchers [46].

3. Future Implications

Clinical research can be defined as any type of research conducted to find a solution to a clinical problem. The solution in most instances would be a way to diagnose, treat, and manage the patients.

Since there is no vaccination available for many infectious diseases like Dengue, human immunodeficiency virus (HIV) infection, and Hepatitis C (HCV) viral infection, among several others, the knowledge of clinical research could pave the way forward to solve such public health-related problems.

The first step in this regard could be to find a sponsor who can support the idea and go forward in funding until an efficient vaccine is developed. It is the responsibility of the investigators (principal/co-investigators), the institute/research center, the clinical research associates, and the clinical research coordinators who make sure the research is conducted following good clinical practices (GCP), and the auditors, who make sure the research is in tune with the recommendations by the regulatory bodies, like the food and drugs administration (FDA), the central drugs standards control organization in India (CDSCO).

Recent clinical research evaluated the potential of mRNAs as vaccines against some chronic and recurrent infections like HIV, the herpes simplex virus, and respiratory syncytial virus (RSV) [47]. A new HCV vaccine is currently under trial, which proposes and tests a novel hypothesis that the T lymphocyte-mediated immune response alone can prevent chronic HCV infection [48].

HCV vaccine development is a potential idea for future clinical research because the patients with HCV do not necessarily develop symptoms, may transmit infections to others, and chronic infections can cause hepatocellular carcinoma (HCC), and other morbidities.

Influenza viral infection is another infection, that causes seasonal flu and results in severe morbidity and mortality. The virus in this case is highly variable, and therefore there is still no reliable vaccine available. This is mostly because the virus can change/modify the antigens.

Recent research had reported a systematic review of the available studies on influenza virus vaccination. The randomized control and the quasi-controlled trial studies were selected for a systematic review to identify the most efficient available vaccine.

This study searched the Cochrane database for clinical trials, the MEDLINE, Embase, the world health organization (WHO) International Clinical Trials Registry Platform, and the ClinicalTrials.gov websites for the selection of studies.

This systematic review concluded that there were some adverse events associated with the vaccination that include an increase in fever, nausea, and vomiting. Also, the benefit of vaccination among the susceptible population like pregnant women and children was found to be modest [49].

The potential applications of clinical research are evident from the experiences of the current pandemic caused by the novel severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) resulting in the extremely complex Coronavirus disease (COVID-19) [50].

4. Conclusion

Clinical research is of different types and is pursued to address several public health-related issues that include but are not limited to the emergence of novel microbes, new diseases, unavailability of effective therapeutic interventions against existing diseases, and antimicrobial resistance. The available literature clearly points to the fact that several issues continue to plague the public health and healthcare systems. This is even more evident by the current experiences of the pandemic that led to geographical, social, cultural, and economic crises throughout the world. Through clinical research, we can find a way to overcome several such problems. Considering the financial limitations and manpower, increased collaboration between the countries both in the research and development and the pharmaceutical manufacturing areas could pave the way for better tomorrow in terms of human health, and the environment.

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