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Review Article

Why New Drugs, Treatments, and Medical Devices Still Needs to be Tested Clinically Before Making it Available in the Market?

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Abstract

Objective

Testing a new drug, treatment, and medical device clinically is critically important before prescribing it to a patient. Not determining the drug's safety and efficacy through clinical trials might impose life threatening outcomes on its consumers. The research paper describes the critical factors associated for testing any new drugs clinically, as limited research is performed in this field of public health.

Study Design

A qualitative systematic literature review was performed by mining relevant original peer reviewed research papers as well as some online resources like MedlinePlus due to limited availability of studies on such a critical topic.

Methods

The databases used were Web of Sciences core collection, PubMed, Google Scholar. The keywords used to search research papers were "clinical trials", "testing new drugs", "history of testing drugs", "evidence-based medicine".

Conclusion

Drugs which are prescribed to critical target population like pregnant women and children should be more often clinically tested if possible as majority of them are available in the market without Food and Drug Administration (FDA) approval. The abusive potential of any new drug could end up taking

lives of innocent individuals. More evidence-based medicine can help translate research results on a heterogeneous population efficiently.

Keywords:
clinical trials; new drug testing; evidence-based medicine; public health

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Introduction

Today, more emphasis is given to translational research especially in the oncology therapeutic area because of its higher failure rates.[1] Clinical trials are one of the ways through which research is translated to provide evidence-based results. “Clinical trials are research studies that test how well new medical approaches work in people. Each study answers scientific questions and tries to find better ways to prevent, screen for, diagnose, or treat a disease. Clinical trials may also compare a new treatment to a treatment that is already available.”[2] We might have several questions like why clinical trials are required and why would a regulatory agency like Food and Drug Administration (FDA) regulate it for any new drug before approving it for market circulation? FDA’s mission is to protect and promote the health of the public. Concerning drugs, biological products, and medical devices, this translates into ensuring reasonable product safety while also facilitating the translation of scientific innovations into commercial products.”[3]

Historical Background

A lot of times questions regarding the need for clinical research, clinical trials and the purpose of it arise. Looking back at the history about trying and testing new drugs is worthy while answering these questions. The most inhumane was the Nazi experiment conducted during world war two at Nuremberg camp on camp prisoners. [4]It was followed by unethical practice in The Tuskegee Syphilis Study, 1932 to 1972 where the African American participants were kept in blind regarding correct treatment and eventually died[5]. There are also cases in which the participants were one of the family members while trying new drugs/treatment procedure. To name some are “The Nobel laureate Gerhard Domagk (1895–1964) discovered prontosil sodium (a sulfonamide) who first tested it on his 6-year-old daughter who had contracted a severe streptococcal infection from an unsterilized needle and Johann Jorg (1779–1856) swallowed 17 drugs in various doses to record their properties, are only two among many such instances.”[6] .

The reason behind the development of Nuremberg code, Good Clinical Practices as well as Belmont report is the past inhumane activities performed for experimentation on human subjects participating with a will or outside willingness in cases where they are blindfolded. It is the basic human birthright

to live their life happily and healthy. The article 5 of UN charter declaration states that "No one shall be subjected to torture or cruel, inhuman or degrading treatment or punishment." [7]

There always exists a need for research which should be valid and tested before trying it actually on human subjects. Several experiments which are pre-clinical and tested on animal subjects are performed before trying any drug on human subjects to check the safety and efficacy of the drug to avoid severe adverse reactions.[8] Hence there should not be any resistance in recruiting human subjects for testing any new drug, treatment, and device when the need arises. The safety level determined by pre-clinical studies will help avoid adverse outcomes in human subjects to some extent. The following paragraphs would elaborate three ethical aspects which need to be considered while making a decision for clinical trials.

Hippocratic Oath: Not harm by any Means

Many times, certain off-label drugs are used for critical lifesaving purpose or tertiary prevention which is not described as per FDA approval. The drugs which are psychotropic and are used for treating pediatric patients often have limited information regarding their safety and efficacy. "Many children in the USA are prescribed psychotropic drugs that have not been fully investigated in pediatric clinical trials. The common practice of prescribing psychotropic drugs off-label poses unknown and potentially serious short- and long-term consequences for these children." [9]. Certain drugs are difficult to test on a particular group of populations like pregnant women and children because of their susceptibility to developing severe adverse reactions faster over a normal healthy adult. The other major factor, by taking into consideration the Hippocratic Oath is, right to autonomy and respect. The child's ability to make decisions for his/her treatment like clinical trials is not developed and, in such cases, a caregiver has the authority to decide about whether to participate or not in the clinical trials for the drug which is tested. It is one of the major reasons why there are limited drugs available as well as certain off-label drugs available in the market. On the other hand, not considering the clinical trials of certain population targeted drugs seems to be not abiding by the oath. Making these drugs available in market on the name of rarity of recruitment availability in certain target population like children and pregnant women, is completely unethical. Those populations who do not fall into available treatment options and the last resort is clinical trials, should always be considered for clinical testing of such drugs. Only through clinical testing, effective translational research results of a particular drug could be made available and a safety margin for a particular drug could be determined.

Moreover, the psychological and physiological dependence of any drug could only be determined through clinical testing which could end up saving such a population group, if being predetermined before prescribing.

There are oncology drugs which are used to treat cancer but are available in market at expensive rates. The reason besides its high rate is the cost associated to test the drug clinically, get it approved by regulatory bodies and finally make it available in the market. [10],[11] The whole research and development of the drug cost a lot. [11] Then why not make it available outside of clinical trials? Autonomy, beneficence, non-maleficence are some of the basic ethical principles

which every medical practitioner should keep in mind while performing clinical research. While trying to save some monetary resources we are risking innocent lives by making the drug available without getting it approved by the regulatory bodies like FDA. Patients trust their physicians as well as drug manufacturing companies regarding prescription medications. In such circumstances, we are ignoring ethical principles and harming patients by making such drug available without FDA approval. The potential drug might turn into a nightmare by affecting the consumer adversely and might cause death, be it children or grown adult. Testing a new drug pre-clinically as well as clinically gives us more information about its safety and efficacy as well as adverse reactions if any. The clinical trials not only act as gatekeepers like regulatory bodies of respective countries, for any new drug approval but also reflect great clinical data which can help support future trials.

Every Individual Differs Genetically so Does the Drug Response

No single person is identical genetically in this world. Every individual differs regarding behavior, lifestyle, habits, as well as the history of their disease [12] and so, does the treatment response. If a drug

is made available outside of clinical trials without testing its efficacy and response to human subjects, the drug might fail in terms of providing effective treatment response. To better translate the research outcomes in the real-world setting, one might want to test the intervention on original genetically heterogeneous human subjects over others like laboratory cultured cells/tissues or animals. Studies which use animals as subjects to test the drug efficacy and response are known as pre-clinical studies. The drug is first tested on animals, and a safe dose is measured. The animal subjects used for testing the drug for a particular disease resemble the human counterparts in a majority of the ways. They have similar liver, heart, and brain functioning activities as well as cellular tissue components.[8] Humans resemble chimpanzees by sharing 96% of the 30,000 genes and rest 1200 genes differ what makes us humans.[13] Though animals are used as subjects replacing a human, they react in a different way than humans do to different drugs.

The reason behind this might be different genetic complexity. The human tissue formation is more complex over animal tissues regarding genetic composition.[8] The human subjects differ amongst themselves as well. Females differ from males in both human and animal counterparts, and so does their response. [14] Hence, even though a drug is tested on human subjects, its efficacy and dose-response might differ from person to person or from animals to humans. The basic requirement for any research to be translated into the real world is the accuracy of data regarding efficacy, severe adverse reactions as well as safety. The errors made at grassroots level might turn into a greater failure at the highest level of research once it approaches at that point. For any research certain factors need to be kept in mind like barriers as well as surrounding environment. Research results are tested under strict controlled environment hence it differs regarding translation to a real-world setting.[15]Due to such existing gaps between research and the real world, we have faced certain failure for achieving expected drug efficacy and response in human subjects.

Helps Translation of Research Results Into Real World

“Knowledge Translation has been defined in various ways but has generally focused on the application of knowledge. For example, the Canadian Institutes of Health Services Research (CIHSR)[6]has described KT as the complex process of the ‘exchange, synthesis and ethically-sound application of research findings within a complex set of interactions among researchers and knowledge users.”[16] As mentioned earlier in this paper, translation of research results achieved in the laboratory regarding new drug testing should always be achieved in a real-world setting for its expected outcomes. The purpose of clinical trials itself answers the questions for knowledge translation. We have failed regarding demonstrating implementation of discoveries made.[17] But clinical trials data provide us with strong evidence for translational medicine regarding testing a new drug which has passed the pre-clinical trial tests.

Translational research not only opens the door for effective implementation but also for cost-effective research and development of any drug into the market. The cancer drugs are one such area in which more clinical trials are required to be performed on a broad spectrum of the population to achieve the research results of the laboratory into the real world. Oncology is one such area which is not defined in a certain way like diabetic condition is. Every cancer tissue is different regarding its complexity as well as composition. In such situations to cure it, we need to come up with a personalized treatment plan. More and more clinical trials can help us gain in-depth knowledge in this therapeutic area regarding translational medicine. Moreover, lack of certain Adverse Drug Events information about psychotropic or anticonvulsant drugs, might increase rate of poor drug adherence.[18] Clinical trials allow documenting Adverse Drug Events which are proven and parents or concerned individual might be able to trust life saving drugs more and adhere to it. Even after making efforts to develop a protocol for a clinical trial, sometimes a need for increase in headcounts for sample size rises due to criticality of the type of drug and need for a specific target sample. In such cases, raising awareness about clinical trials in lay-man terminology in the form of advertisements could also enhance headcounts of required sample population. A lot of the times general population is unaware about these last lines of treatment option and in such cases, storytelling communication strategy could be used to enroll relevant subjects. The only thing to be kept in mind is the way population perceives those storytelling concepts, rather they have access to modern technology which has applications like social media accounts.[19]Clinical

trials including adverse drug events help doctors or physicians to decide whether to prescribe certain drugs to certain susceptible patient or not.[20] Doctors might help mitigate more cases of Adverse Drug Events by getting more information through such clinical trials. Hence, clinical trials might turn to be more positive in terms of acceptability amongst Physicians as well as critically ill patients. Not only just medicines but the effect of certain electronics on the human body or human genes might open the future doors for better quality of life through better designing of the electronic. The effect of cellphone radiation on the human body, for instance is yet to be clarified; clinical trials of cellphone radiation on the human body or genes might help mitigate its effect.[21]Hence clinical trials hold a future of forecasting several effects of drugs and or equipment's which are yet to be explored by just observational studies.

Conclusion

Looking at the history of new drug development and research, we do not want to sacrifice innocent lives by not testing new drugs pre-clinically. Experiments like the Holocaust of Nazi's on twins or be it Tuskegee study, have warned us about the psychological, social as well as physical outcomes on the individual. We are not looking for something which can save our lives at the cost of other human beings. Nor do we want the consumer to start abusing the drug out of physical or psychological dependence ability of the new drug. Predetermination of side effects of any drug can greatly save the infants and other population's life. The current study takes into consideration Clinical trials in general over specific therapeutic area. Future studies might want to consider other factors regarding optimizing specific therapeutic area clinical trials, the feasibility of the particular sample subjects as well as animal models, and the feasibility of the drug availability at affordable prices.

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Competing Interests

The authors declare that they have no conflict of interest

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