Review Article

Major Causes Associated with Clinical Trials Failure and Selective Strategies to Reduce these Consequences: A Review

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Abstract

New drug development is a highly regulated and complex process that involves the pharmaceutical industry, academic institutions, and government agencies' collaborative work. In pre-clinical testing, statistics indicate that out of 5000 compounds only five enter and evaluated in human clinical trials, moreover, only one drug is approved for human use. The whole process of drug development takes around $2-2.5 billion and a time of 12-15 years to complete. Around 50% of investigational compounds fail during the development phase of clinical trials. Despite numerous scientific and technological advancements in research and development, many clinical trials fail to develop new, safe, and effective drugs. Approximately, 70% of clinical trials fail in phase 2; whereas, the failure rate of confirmatory trials (phase 3) is around 50%. Tufts center for the study of drug development evaluated the three most common factors behind clinical trial failure-safety, efficacy, and deficient funds. Success-failure of a trial is also associated with other factors like a new molecule, molecular size, and therapeutic efficacy. As drug development involves numerous lives and billions of investments, one failed trial affects the subject's quality of life by physical/social consequences and huge losses to pharmaceutical companies. To reduce the failure rate, many biopharmaceutical companies have opted or established their own more disciplined protocol, portfolio, and progress review frameworks. These strategies reduce the chances of errors during drug development and help in clinical trials' success rate.

Keywords: Clinical trials failure, Drug development, Financial impact, 5R framework

Introduction

The development of a new drug for the treatment of any disease takes years of collaborative research on the part of the pharmaceutical industry, academic interests, and government regulatory authorities [1]. Drug development involves precise testing and optimization of compounds to find the most effective drug. This testing is done in vitro (in cells) and in vivo (in animals) to produce a drug that is safe, efficacious, and passes all the regulatory requirements [2]. The new drugs, medicinal devices, and biological agents cannot enter the market without the review and approval of regulatory authorities. Each country has its own regulatory body like Central Drugs Standards and Control Organization (CDSCO) in India; Medical and Healthcare Products Regulatory Agency (MHRA) in the UK; Food and Drug Administration (FDA) in the USA; Union- European Medicines Agency (EMA) in Europe, etc. that govern the approval process. The US system of new drug approval is the most rigorous all over the world [1].

The Center for Drug Evaluation and Research (CDER) is the FDA's largest center whose responsibility is to ensure the efficacy and safety of drugs. Statistics indicate that out of 5000 compounds, which have been evaluated in pre-clinical testing, only five entries and are evaluated in human clinical trials, and out of these five, only one drug is approved for human use. On average, it takes around $2-2.5 billion and a time of 12-15 years for a compound to pass from all stages of drug development and be an approved drug available in the market [3].

Material and Methods

We performed a literature search from reputed and indexed journal data sets including PubMed, Scopus, and Institute for Scientific Information Web of science from December 2019

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How to cite this article: Arora A, Nain P, Kumari R, Kaur J. Major Causes Associated with Clinical Trials Failure and Selective Strategies to Reduce these Consequences: A Review. Arch Pharm Pract. 2021;12(2):45-53. https://doi.org/10.51847/YJQDk2wtgX

to June 2020 utilizing special keywords, for example, clinical trials, stages of drug development, clinical trials failure, strategies for improvement, etc. In the underlying search, all articles that had these keywords in their titles or abstracts were picked, and other disconnected articles were wiped out. Bibliographies of retrieved articles for additional references were also searched. The clinical and pre-clinical studies were highlighted. To decrease bias all authors performed the search, selection of papers (research, review, and meta-analysis), and extracted data of articles independently.

Stages of Drug Development

The complexity in drug development has increased manifolds over the past 40 years, requiring preclinical testing, Investigational New Drug (IND) applications, and completed clinical testing before marketing approval from the Food and Drug Administration (FDA). Generally, NDAs or biologics license applications (BLA) are reviewed comprehensively before approval, and then drug performance is resubmitted to regulatory agencies for post-marketing studies. The overarching goal is to bring more efficient and safer treatments to the patients as quickly as possible after a thorough medical evaluation. There are different critical steps in the drug development process, including many phases and stages within each of them **(Figure 1)**. These various phases and stages develop an in-depth understanding of the entire process [4, 5].

- Drug discovery and product characterization
- Formulation and development
- Drug pharmacokinetics and drug deposition
- Preclinical toxicology testing
- IND application
- Bioanalytical testing
- Clinical trials
- Regulatory review
- Drug marketing
- Postmarketing surveillance

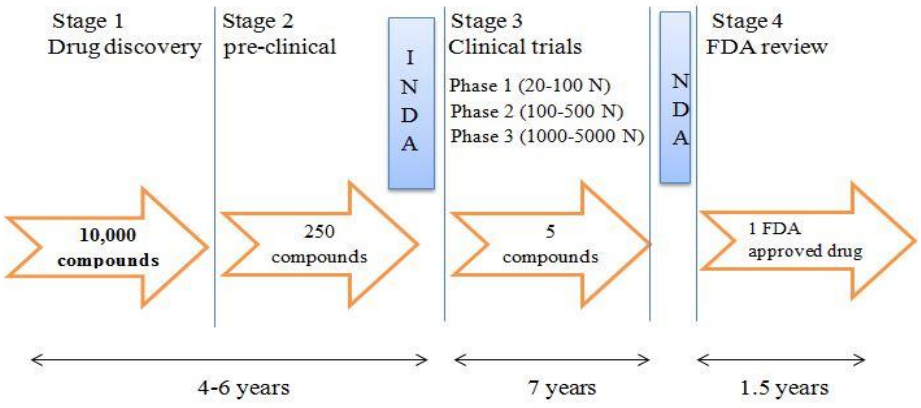

Figure 1. Drug Development Process, Adapted from Pharmaceutical Industry Profile [4, 5]

Clinical Trials: Testing of Medicinal Products

According to WHO, clinical trials are type of research that study new treatment compounds and evaluate their effects on human health outcomes [5, 6]. Clinical trials are usually done in five phases with increasingly precise procedures in every phase. Compounds that are ineffective or insufficiently safe at one phase cannot proceed to the next phase. Any new drug has to pass pre-clinical studies before it enters clinical trials. Pre-clinical studies are done in vivo (animal populations) and in vitro (laboratory). In vitro substrate or animal, subjects are administered with different dosages of the study drug to obtain pharmacokinetic parameters, toxicity, and preliminary efficacy to assist pharmaceutical organizations and researchers in deciding whether it is advantageous to proceed with further testing. Before the initiation of a trial in human subjects, it is important to consider the problems, specific aims, and risk-benefit ratio of drug therapy and the chosen options must be ethically justified and scientifically sound [7, 8].

Phase 0: Phase 0 is first in human, exploratory trials which are conducted according to US FDA 2006 guidelines on exploratory investigational new drug studies [9]. These trials are also known by the name of micro-dosing studies in humans, which were designed to accelerate the drug development process by establishing whether the promising drug shows its effect in human subjects in comparison with the results from pre-clinical studies. In phase 0, a few human subjects (10-15) are administered with a single sub-therapeutic dose of the trial drug to collect preliminary information on the drug's pharmacokinetics and pharmacodynamics. Phase 0 trials do not give any information on the safety or efficacy of the drug as the dosage administered in the human subjects is below the therapeutic range. The main purpose of carrying out phase 0 studies by

the pharmaceutical companies is to rank the drugs according to the best pharmacokinetic parameters in humans and to take that drug into the next phase for further evaluation [3].

Phase 1: Phase 1 studies involve the drug's safety profile testing including its safe dosage range. These tests involve 20-80 healthy volunteers and take around one year to complete. In some circumstances, real patients are also involved, like patients with a lack of other treatment options or patients with end-stage disease. This is mostly done in oncology and HIV drug trials. The prime objective of the phase 1 study is to determine the safety of the investigational drug and the dosage that induce side effects. In this phase, ADME (Absorption, Distribution, Metabolism, and Excretion) of the drug and its duration of action are also determined. However, phase 1 studies are not designed to evaluate efficacy but the drug's therapeutic benefit can be possibly observed if the effective dose range is determined. Typically, the dose range of the drugs used in Phase 1 trials is decided by the investigator, based on the outcomes of preclinical animal studies. Investigators use a wide range of doses to evaluate the maximum tolerated dose and a dose that can be used in phase 2 study design. The pharmacological factors addressed in phase 1 study such as rate of metabolism, half-life, and rate of excretion of the drug are helpful in the development of a proper dosage regimen [3, 10].

Phase 2: Phase 2 study aims to evaluate the initial effectiveness of the study drug. In this phase, 100-300 volunteer patients are enrolled (subjects with the disease) and take around two years to complete. Phase 2 trials are initiated, once the study drug's initial safety is confirmed in phase 1. This phase also demonstrates further safety assessment of the study drug and how well the drug works in a large number of patients. The main concern of investigators in performing phase 2 trials is to demonstrate Minimum Effective Dose (MED) and confirming Maximum Tolerated Dose (MTD). Moreover, these trials also help investigators discovering effective dosage regimens. Phase 2 trials are closely monitored and well-controlled and can be conducted simultaneously with phase 1 trials thus, evaluating both efficacy and safety. Sometimes phase 2 trials are divided into two phases i.e. 2A and 2B. Phase 2A specifically addresses the dosing requirements, thus concerned about the safety of the study drug whereas, phase 2B is designed to examine the efficacy of the study drug. By the ending of phase 2 trials, the investigator knows exactly at what dosage the study drug is effective as well as safe [6, 10].

Phase 3: These are also termed confirmatory trials. Phase 3 trials are comparatively longer, most difficult, and expensive than other phases. The average duration of study is two to three years and usually involves 1000-3000 patients with the disease. The patients enrolled in the study are closely monitored to determine efficacy and identify any adverse event/adverse reaction. The main purpose of performing trials on a large population is to unmask any long-term side effects (rare or common) and to prove that the drug is statistically effective. These trials are controlled and double-blinded to prevent bias. Minimum two successful phase 3 studies are required, which can demonstrate the drug's safety and efficacy, to present data and getting approval from a regulatory authority. After the study, if the drug proves satisfactory outcomes (both safe and effective), the results of trials are combined to a large document with a comprehensive description of the manufacturing process, methods, shelf life, formulation details, results of animal testing, human study and submitted for review to the regulatory authority of that country. Once the submission is reviewed, it is either rejected, hold or the sponsor gets approval to market the drug. The drug can only be marketed with proper guidelines and recommendations under FDA norms. In case of any ADR or ADE reported anywhere, the drug has to be immediately withdrawn from the market [11, 12].

Phase 4: Phase 4 trials or Post-marketing Surveillance (PMS) are conducted after a drug is marketed, to provide additional information about the drug's safety and efficacy. Phase 4 studies are usually non-experimental or observational. The main aim of PMS is to evaluate long-term side effects in a heterogeneous population. Phase 4 studies address the factors which were not covered in the last 3 phases such as (rare adverse events which occur after prolong time, study drug interactions with other drugs, drug effect in new-age groups, races or certain population group which were not enrolled in the previous phases e.g. pregnant women). Negative results discovered in phase 4 might result in the drug getting withdrawn from the market, no longer sale, or certain use restriction [12].

Reasons Attributed to Clinical Trials Failure

Pharmaceutical companies worldwide strive for the development of new drugs and novel therapies. Despite numerous scientific, operational, and technological advancements in R & D that would lead to an increase in the success rate of drug development, many clinical trials fail to develop new, safe, and effective drugs. Approximately, 70% of clinical trials fail in phase 2 whereas, around a 50% failure rate in confirmatory trials (phase 3) [13, 14]. Many research groups analyzed failed trials and uncover potential drivers responsible for clinical trial failure. Tufts center for the study of drug development evaluated clinical trials from the year 2000-2009 in a study and found the three most common factors behind clinical trial failure [15].

- Safety- unexpected/serious adverse event
- Efficacy- drug fails to meet efficacy endpoint
- Financial- lack of funding

Lack of Safety and Efficacy: In the era of clinical research, safety and efficacy are the key factors of successful drug development. Inadequate efficacy is considered as the primary driver for clinical trial failures. In a study done by Hwang *et al*., out of 640 phase 3 trials, 54% of trials failed in the phase of clinical development and 57% of those were

failed because of inadequate efficacy [16]. Sometimes due to many reasons, efficacious drugs fail to demonstrate adequate efficacy. These include inappropriate statistics, flawed study design, or unpowered clinical trials. The other major cause of clinical trial failure is the safety of the study drug. Some studies assess that 17% - 20% of phase 3 trials were failed due to safety issues [16]. Safety of drug is assessed in every phase of the clinical trial, but safety issues mostly arise with larger populations i.e. phase 3 or phase 4 (Postmarketing) [17]. Identification of safety issues is sometimes complicated, as the adverse events observed in patients do not match with the events physician is concerned about, e.g. in a study by Henon *et al*. 27 phases 1 trial were analyzed between the year 2014-2015. Before initiation of these trials, patients were most concerned and feared adverse events like vomiting, hyperglycemia, and haematuria and after trials, some patients experienced the same events along with fever, dizziness, and personality change [18]. Even the physicians involved in these trials were not concerned about these events. Sometimes rushing studies into the next phase after completion of the previous one result in less time or no time in addressing the safety issues properly [19]. It is critical to consider safety as a primary concern at each phase of clinical research as it increases the cost to uncover safety issues of a drug at every stage, including PMS [20].

Financial Impact: According to a study, 22% of phase 3 clinical trials failed due to insufficient funding [16]. The cost required to complete the whole drug development process i.e. (from the discovery stage to marketing the drug) may vary but estimates around $2.5 billion [21]. Pharmaceutical Research and Manufacturers of America (PhRMA) estimated around $42,000/ patient in 2013 with an overall expenditure of 10 billion dollars on 600,000 patients enrolled in 1680 phase 3 clinical trials [22]. A study done on hospital-acquired bacterial-pneumonia estimates cost, for 1000 patients, in 200-sites, was around $89600 / patient with the cost being the primary factor for the failure of the study [23]. Many trials remain unfunded due to large financial burdens and might lose the opportunity to produce a positive outcome, comprising ethical issues regarding the involvement of subjects [24].

Therapeutic Efficacy: A study by the Biotechnology Industry Organization (BIO) and Biomed Tracker (BMT) demonstrates the variation in failure rates of clinical trials due to therapeutic indication. Out of these trials, the highest failure rates were found in cardiovascular and oncology trials. When oncology and non-oncology trials were compared, the success-failure ratio of these indications varies more significantly, specifically at later phases. During phase 2 or phase 3 to regulatory submission, the failure rate of oncology trials is more as compared to non-oncology trials i.e. 29% failure rate for non-oncology and 48% for oncology trials [25]. However, 97% of oncology trials fail to get FDA approval specifically due to toxicity issues or inadequate efficacy [26]. Another most common reason for the very less success rate of oncology trials is off-target toxicity/interactions by most cancer drugs [27].

Molecule's Size: Tufts CSDD study found that the probability of failure for small molecule clinical trial is more as compared to large molecule trials. Out of all phase, 3 trials analyzed, 39% of trials involving small molecules failed to progress from phase 3 to the regulatory application phase (61% success rate) whereas trials involving large molecules have a failure rate of 26% (74% success rate). The study also demonstrates that, within subtypes of large molecules, the success rate for monoclonal antibodies and recombinant proteins were overall similar, but moving from phase 3 to the regulatory application phase, the success rate of monoclonal antibodies is more than recombinant proteins (87% success rate for monoclonal antibodies whereas 66% for recombinant proteins [15, 28].

Major Clinical Trials Failure

Atabecestat: Atabecestat is a molecule under trials for the treatment of Alzheimer's Disease (AD) by Janssen Research and development. This trial was failed due to a lack of safety during Phase IIb/III. The amyloid hypothesis of AD suggests the accumulation of beta-amyloid pathological forms (Aβ), a component of a large protein known as an Amyloid Precursor Protein (AAP). There are mainly two enzymes involved in the production of Aβ: β-secretase, and γ-secretase. β-secretase which is also known as β-site amyloid precursor protein cleaving enzyme 1 (BACE1), is the primary target, and inhibition of BACE1 is one of the important therapeutic approaches in the treatment of AD. This led to the development of many potent BACE1 inhibitors. Many of these drugs entered the late stages of clinical trials but failed at different stages [29]. Atabecestat (JNJ-54861911) was developed by Janssen R&D (Johnson and Johnson) as a BACE1 inhibitor for the treatment of Alzheimer's disease. In 2013, atabecestat enters phase 1 trials. The study initiated to evaluate the safety and tolerability of the drug in healthy older people (NCT01887535), Janssen discovered that atabecestat lowered levels of beta-amyloid in CSF in the brain and spinal cord. Another trial evaluated the drug's safety and tolerability and ability of the drug to lower β-amyloid levels in CSF, in subjects who are at risk of developing the disease but with no symptoms (NCT02360657). No results were published after the completion of that study. Phase 2 trial of atabecestat (NCT02406027) initiated to evaluate the drug's safety in patients who were at an early stage of the disease. Patients, who completed phase 1b/II trials and wish to continue treatment, were enrolled in the study. Another phase 2b/ III trial was conducted by Janssen (NCT02569398), to compare the ability of the drug in 596 subjects with no symptoms but who were at risk of developing AD. Further clinical development of atabecestat was halted by Janssen and both phase IIb/III and phase 2 studies were stopped after the elevation of liver enzymes in study participants [30-32].

Dexmecamylamine: Dexmecamylamine, molecule undergone clinical trials for the treatment of depression, but the study failed in phase III due to lack of efficacy and safety. Depression, common mental disorder, described as anger/loss of anger, feeling of sadness, irritability/loss of expressions, etc. These symptoms generally interfere with daily living, i.e. cognitive abilities, behaviour, sleep patterns, etc. SSRI (Selective Serotonin Reuptake Inhibitors) and SNRI (Serotonin-norepinephrine Reuptake Inhibitors) are first-line therapies in treating depression. These drugs work by increasing the amount of neurotransmitters-norepinephrine and serotonin in the brain [33].

Researchers had hypothesized that dexmecamylamine could activate certain receptors like nicotinic neural receptors and potentially treat symptoms of depression by neutralizing these receptor's activity [34]. A phase 2 trial was initiated in 2009, randomized 270 participants to receive either dexmecamylamine or placebo for a time of eight weeks. The results of the study were in favour of dexmecamylamine i.e. more improvement was seen on the standard depression scale in patients who receive dexmecamylamine as compared to those who receive a placebo [35]. With positive phase II results, dexmecamylamine enters phase 3 studies. Four studies were initiated with a total of 614 participants who do not get any relief with standard SNRI or SSRI therapies, were randomized, and receive either dexmecamylamine or placebo with their SNRI/SSRI therapy. After 2 months no difference was observed on the standard depression scale in patients of both groups (demecamylamine or placebo) in any study [36-38].

MAGE-A3 Vaccine: Broadly, there are two forms of lung cancer i.e. small cell and Non-small Cell Lung Cancer (NSCLC). Currently, there are three treatment options for NSCLC- chemotherapy, surgical removal, and radiation therapy, but still, there is a low long-term survival rate [39]. According to recent advancements in cancer research, harnessing the body's immune system is potential in the treatment of NSCLC. Certain cancer cells exhibit antigens (surface molecules) which could be targeted by cancer vaccines, to preserve healthy cells [40]. MAGE-A3 is one of the examples of tumour-specific antigens which is present on certain tumour cell's surface. Unlike normal lung cells, MAGE-A3 is expressed by around 33% of NSCLC, therefore making it an ideal target for NSCLC therapies.

MAGE-A3 vaccine was evaluated in a phase 2 study, as a treatment regimen for NSCLC in MAGE-A3 positive patients. Following surgery, a total of 182 patients were enrolled and randomized to receive either the MAGE-A3 vaccine or placebo 13 times over 27 months. No significant improvement was observed statistically in overall survival and disease-free survival among patients, who receive the MAGE-A3 vaccine [41]. Even after promising results, the sponsor propels the vaccine in phase 3 trials [42]. In phase 3, a total of 2272 NSCLC patients, who were completely MAGE-A3 positive, were randomized to receive 13 I.M. injections of either placebo or vaccine [43]. Statistically, no significant difference in disease-free survival was observed in patients who receive the vaccine (60.5 months) as compared to placebo (57.9 months) [43].

Torcetrapib: High cholesterol or hyperlipidemia puts the patient at risk of developing cardiovascular (CV) diseases. In different ways, cholesterol is accumulated in the bloodstream. Mainly two types of cholesterols- HDL-high density lipoproteins, which is also referred to as "good cholesterol" because levels of HDL are inversely proportional to cardiovascular risks i.e. high HDL- low CV risk whereas this concept is opposite in the case of LDL. Low-density lipoproteins are also referred to as "bad cholesterol" because high LDL level is associated with increased CV risk [44]. To minimize CV risk in patients, consequently, clinicians aim to reduce LDL cholesterol and increase HDL-C. Conversion of HDL-C into LDL-C is done by enzyme Cholesteryl Ester Transfer Protein (CETP). Preclinical data and phase 1 proves that torcetrapib works by blocking CETP, thus lowering LDL-C and increasing HDL-C levels. The drug enters Phase 2 and performed well in trials on a measure of HDL-C and LDL-C. A small rise in blood pressure was observed in some patients on torcetrapib treatment [45, 46]. For development and further testing of torcetrapib, Pfizer spend around $800 million, claiming that it might be the most important development in clinical research [47, 48].

Torcetrapib enters phase 3 trials were over 15000 patients with a history of stroke, CAD, peripheral artery disease, or diabetes were randomized to receive either torcetrapib or placebo with a statin. Time of occurrence for any major CV event (stroke, cardiac arrest) was the primary outcome whereas secondary outcome measures were blood pressure and cholesterol levels. Along with CV events, LDL-C levels decreased and HDL-C rises significantly in patients who were on torcetrapib compared to those who received placebo. With these outcomes, the drug was proved dangerous and not shown effective. Total 58% of patients, who were on torcetrapib die from any cause whereas, 25% of patients suffering from major CV events, compared to those who received placebo. Blood pressure levels in the torcetrapib group were significantly high than placebo [49]. The study was halted because of unexpected safety issues with torcetrapib [47].

Semagacestat: Dementia is the progressive decrease in memory and other cognitive aspects. Alzheimer's disease (AD) is a fatal and progressive form of dementia, occurring when neurons in the brain start dying prematurely. The amyloid hypothesis of AD suggests the accumulation of beta-amyloid pathological forms (Aβ), a component of a large protein known as an Amyloid Precursor Protein (APP). There are mainly two enzymes involved in the production of Aβ: β-secretase, and γ-secretase [50]. Researchers believed that semagacestat acts by blocking gamma-secretase activity

therefore could have an important role in the treatment of Alzheimer's [51]. A Phase 2 study of semagacestat initiated to evaluate the drug's effect. In the trials, semagacestat shows a significant reduction in β-amyloid concentration in blood among patients who received semagacesat for 14 weeks [52].

After phase 2 completion, the drug enters phase 3 studies where around 1500 patients were randomized to semagacestat or placebo for 18 months [53]. Change in cognition was the primary outcome, in ADAS-cog and ADCS-ADL to measure function from baseline to 18 months. Patients who took semagacestat daily experienced worse cognition and overall functioning during the trial compared to patients who took a placebo. Treatment with semagacestat shows a significant decrease in amyloid-beta concentrations along with worsening of cognitive functions, quality of life, global functioning, and daily living activities. Patients who took semagacestat also faced more ADE - including skin cancers, infections, and total cancers as compared to placebo. Patients who received semagacestat were at double risk of skin cancer compared to a placebo group. Before completion, the company halted the trial due to safety concerns [53].

Figitumumab: Figitumumab, a monoclonal antibody that was synthesized for the treatment of lung cancer. Broadly, there are two forms of lung cancer i.e. small cell and Non-small Cell Lung Cancer (NSCLC). Currently, there are three treatment options for NSCLC- chemotherapy, surgical removal, and radiation therapy, but still, there is a low long term survival rate [39]. Growth factor- IGF-1R contributes to the development and spreading of NSCLC, amongst other cancers [54, 55]. Researchers believed that figitumumab inhibits IGF-1R thus could play an important role in the treatment of cancer. In animal testing, figitumumab enhanced anti-cancer effects of other standard chemotherapies, whereas in phase 1 studies figitumumab demonstrates its effect by showing antitumor activity and inhibiting target pathways against different forms of cancers, specifically NSCLC. Phase 2 trials randomized NSCLC patients on paclitaxel and carboplatin (standard drugs) or figitumumab with carboplatin and paclitaxel, resulting in higher response rates in patients receiving figitumumab with standard drugs then paclitaxel and carboplatin alone [54, 56].

With these results, figitumumab enters phase 3 where two trials, with 1264 NSCLC patients, were conducted, to compare figitumumab plus standard therapies with standard therapies alone [57, 58]. Both studies were terminated because figitumumab failed to enhance the survival rate. Moreover, figitumumab plus standard therapies increased the incidence of SAE (serious adverse events), decreased overall survival, and even deaths [58]. Overall, 21% of patients who received figitumumab experienced SAE whereas 12% in patients who received a standard regimen alone. The rate of death in patients who received figitumumab was 5%, whereas 1% in patients with the standard regimen [58]. Pfizer retracted the previous phase data after the early termination of phase 3 trials due to efficacy and safety concerns [59].

Major Consequences of Clinical Trials Failure

There are various significant impacts of clinical trial failure, with the most affecting impact on financial cost and human lives. The first and major negative impact on thousands of human subjects who were enrolled in the research study in the hope of finding a successful treatment option. Analysis done by PAREXEL revealed that approximately 1,50,000 patients were enrolled in the phase 3 trials (2012-2015) which eventually failed. Most of them had diabetes mellitus, cardio-pulmonary diseases, or cancer [60]. Patients who volunteer themselves to take part in clinical trials are either difficult to treat or at the late stage of the disease, with few or no standard treatment options available. Most of these patients do not have enough time and taking part in clinical trials is their last option in a hope of a potential cure of disease or at least prolongation of life. Thus, failure of drug trials has a widespread impact on patients i.e. physically or mentally or both as it may worsen the patient's quality of life, prognosis, and emotional well-being.

The other major consequence of a failed clinical trial is the economic impact. Failure of large trials leads to a great loss to biopharmaceutical companies which increases the material financial burden and contributes to poor capital productivity. Only a few new drugs are getting approved by the regulatory authorities, considering the financial investments in R&D. According to a study, Billion dollars invested on R&D every year, there is approximately a 50% decrease in the number of new drugs getting approved, since 1950 [61]. The financial impact of failed trials often goes beyond investment required in R&D. A study done in 2014, analyzed most impactful clinical trials failure and found that these trials failure results in huge financial loses, termination of programs and jobs as well. Pharmaceutical companies must invest their resources and funds effectively and efficiently to complete the development process successfully [62].

Results and Discussion

Strategies to Reduce the Risk of Trial Failure

To fulfill the growing needs and decrease the chances of trial failure, many biopharmaceutical companies have opted or established their own more disciplined protocol, portfolio, and progress review frameworks.

The 5R Frameworks: In 2011, AstraZeneca evaluates its drug projects involving small molecules over 5 years i.e. 2005-2010, and identified the most significant factors which contribute to project success. By addressing those factors, AstraZeneca developed a framework to improve its R&D procedures to drive its development process and to decrease the chances of failure of its clinical trials especially phase 3. The framework is named as 5R framework which guides its R&D teams to identify the right tissue, right target, right

patients, right safety, and right commercial potential. An additional factor to this framework is the right culture, i.e. where the data and facts are not manipulated and confronted honestly [63].

Adequate Phase 2 Testing: The major reason behind the failure of phase 3 trials is a lack of understanding about the mechanism of action of the drug. To address this issue and increase the success rate of the new molecular entity (NME) during phase 2 trials, Pfizer analyzed 44 phase 2 trials during 2005-2009 to identify key factors associated with the trial's success [64]. By evaluating the results of the analysis, Pfizer developed a framework, which can help the R&D team, determining three significant key elements that reduce the chances of NME to fail in phase 2 and successful moving to phase 3. The framework was named "Three Pillars of Survival" [64].

- Pillar 1 involves the drug's exposure towards the target site of action, necessary to draw out the pharmacological effect of the drug over the desired time.
- Pillar 2 involves the drug's binding to the target, for pharmacological expression and modulation of the target.
- Pillar 3 involves the expression of pharmacology, to examine the mechanism of action.

Rushing to phase 3 without a proper understanding of these key components often increases the chances of phase 3 failures. An adequate understanding of these components overhauls the R&D process and reduces late-stage failures [64].

Adaptive Designs: Clinical trial design has a significant impact on its success. Nowadays, the adaptive design of the trial is gaining momentum to reduce the risk of failure. These designs provide the opportunity to analyze interim data and to check some initial assumptions or uncertainties which were made at outset of the trial [65, 66]. Additionally, these designs provide an opportunity to change course and correct these uncertainties and incorrect assumptions during a trial, in a prospectively organized manner which do not endanger operational integrity and statistical validity of the trial [67].

Biomarkers: According to WHO, biomarkers are defined as any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease [68]. Biomarkers are increasingly used now to assess efficacy more objectively [69]. A particular challenge with the use of these biomarkers in trials is the requirement to validate them as relevant disease-altering endpoints and analyze changes in those endpoints to changes (if any) in disease progression [70]. These enrichment strategies are often used to optimize the study population especially those subjects, who are more likely to respond to investigational therapy [71].

Adaptive licensing, collection of real-time data using wearable devices, master protocols, next-generation sequencing, understanding disease genetics, etc. are some other examples that are opted to reduce failure risk. However, clinical trial failure cannot be eliminated but strategies discussed above in the article, provide sponsors with some tools to minimize failure risk and increase chances of their successful drug development process [72, 73].

Conclusion

Around 50% of investigational drugs/products failed during the development phase, during or after clinical trials. We believe that the current clinical trial failure rate is unacceptably high. It is essential to understand the factors and root causes behind these failures. We carried out this review for a better understanding of clinical trial failure as the majority of failed trials are not published in journals. In our study, we briefly explained clinical trial phases, enlisted factors which are the major cause, and the consequences of clinical trial failure. In addition, we highlighted some examples of major clinical trials failure and some strategies which are being implemented by biopharmaceutical companies to increase chances of trial success rate.

ACKNOWLEDGMENTS: We would like to acknowledge the management of Maharishi Markandeshwar (Deemed to be University), Mullana (Ambala), India for encouragement and necessary facilities support.
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

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