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**Investigating Factors Related to Hepatitis a Outbreak in Ismailia Village, Karun City, in 2019**

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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, 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 |

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**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 [2-5]. 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. 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 European, etc that governs the approval process. The US system of new drug approval is the most rigorous all over the world.

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 enter and 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 [7].

*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](https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm), including many phases and stages within each of them **(Figure 1, Table 1).** These various phases and stages to develop an in-depth understanding of the entire process.[7-9]

* 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

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| **Figure 1.** Statistics on the spread of COVID-19 according to WHO and Johns Hopkins University [32]. |

**Materials and Methods**

According to WHO, clinical trials are a type of research that studies new treatment compounds and evaluates their effects on human health outcomes [9, 10]. 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

*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.

**Results and Discussion**

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.

**Table 1.** Distribution of the participants by selected sociodemographic characteristics

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| **Data** | **No. of participants** | **% (n=600)** |
| ***Gender***  Male  Female | 300  300 | 50  50 |
| ***Participants’ age (years)***  18-25  26-35  36-45  >46 | 275  167  108  50 | 45.8  27.8  18  8.3 |
| ***Education level***  Postgraduate  University  Secondary education  Basic education  Read and write | 60  382  140  15  3 | 10  63.7  23.3  2.5  .5 |
| ***Occupation***  Healthcare worker  Other jobs | 169  431 | 28.2  71.8 |
| ***Socioeconomic status***  High  Middle  Low | 115  251  234 | 19.2  41.8  39 |

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. Atabecestat (JNJ-54861911) was developed by Janssen R&D (Johnson and Johnson) as a BACE1 inhibitor for the treatment of Alzheimer’s disease.

Considering Eq. 1 as follows:

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|  | (1) |

In 2013, atabecestat enters phase 1 trials. The study initiated to evaluate the safety and tolerability of the drug in healthy older people ([NCT01887535](https://clinicaltrials.gov/ct2/show/NCT01887535?term=JNJ-54861911&rank=9)), 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](https://clinicaltrials.gov/ct2/show/NCT02360657?term=JNJ-54861911&rank=1)). No results were published after the completion of that study. Phase 2 trial of atabecestat ([NCT02406027](https://clinicaltrials.gov/ct2/show/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](https://clinicaltrials.gov/ct2/show/NCT02569398?term=JNJ-54861911&rank=3)), 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.

**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. Also, 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.

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**Conflict of Interest:** None

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**Ethics Statement:** None

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