



Why Clinical Trials Fail globally

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Received Date: October 10, 2024; Published Date: November 06, 2024

Abstract

The basic reason for the failure of clinical trials is an inability to demonstrate efficacy and reasonable safety. Most of the clinical trials show failure when a significant sample size of patients is included and when the statistical analysis shows that the new drug either is not efficacious or has high side effects. Companies are also reluctant, to market molecules of similar efficacy as there is always a challenge for marketing. Recently more biologicals have failed, which were developed by various European Biotech companies.

Keywords: Clinical Trial Failure; Phase II & III Studies; Side Effects; Biologicals

Abbreviations

FDAAA: Food and Drug Administration Amendments Act;
USFDA: United States Food and Drug Administration.

Introduction

Progress of Clinical Trial Failure

Most of Clinical studies are designed for desired outcomes and the regulatory approval of the molecules. Clinical trials often fail, however, and prior reports have suggested trial failure rates of around 20%, mostly due to poor accrual. It has been shown that 1 in 6 urologic oncology trials often fail,

most frequently for poor accrual [1]. The drug development needs to ensure a low failure rate in the clinical study. Drug development in recent eras focuses on biologicals. The current data suggests, the drug withdrawal is due to a lack of efficacy or side effects, which need to be reported to regulators as per the Schedule Y of the Drugs and Cosmetic Act, India [2]. The Food and Drug Administration Amendments Act (FDAAA), of US FDA of 2007 requires sponsors to report the results of applicable clinical trials on ClinicalTrials.gov within one year of the trial's completion. The trial results have to be appropriately uploaded for the scrutiny of the FDA (Table 1) [3].

Company	Results	Outcome
Janssen Pharmaceuticals	The HIV Vaccine was tested	Mosiaco Study: 3900 patients were evaluated The regimen did not protect against HIV
Nektar Therapeutics	Rezpeg or Rezpegaldesleukin , failed in Phase II Clinical Trial in Lupus	Phase I data of the study was also inclusive

Kodiak Sciences	Tarcocimab was not better than Eyelea	Unexpected increase in cataracts was observed
Acelyrin	Izokibep – was evaluated in Hidradenitis suppurativa	The drug did not produce significant results, after 16 weeks of treatment
Akero Therapeutics	Efruxifermin-Metabolic dysfunction-associated steatohepatitis, failed in phase 2b study	Raised Hepatic enzymes were associated
BenevolentAI	BEN 2293 was evaluated for eczema, a Pan Trk inhibitor, was not better than placebo in phase II trials	Did not reduce the severity of the itching in eczema
Mirati Therapeutics	Overall survival benefit was not observed in NSCLC. Sitravatinib in phase 3 Sapphire Trial was compared to Docetaxel and Opdivo	Drug failed in Phaw III trials and respective Side effects were also more
Sarepta Therapeutics	Elevidys is being evaluated for Duchenne muscular dystrophy, failed to meet motor function	Failed in Phase III trials with lot of side effects
Bayer Pharma	Asundexian – did not match blockbuster Rivaroxaban. (Xarelto). It was significantly inferior to the oral anticoagulants	Did not have Expected results in Phase III Trials
Merck Pharma	Evobrutinib- BTK inhibitor for Multiple sclerosis was no better than interferon alpha	The annualized relapse rates were high
Roche's Genentech division'	Gantenerumab in Alzheimer's disease was an outcome failure	The ADRs were significantly higher than the comparators
BMS and Nektar Therapeutics	Bempegaldesleukin- nivolumab plus bempeg to Opdivo alone as a front-line treatment for advanced melanoma and showed no improvement for the combination on progression-free survival, objective response rate, or overall survival	The efficacy and safety failed in Phase II A and B studies

Table 1: Drugs that failed in the clinical development plan 2023.

The reasons for clinical trial failure are often multiple. The important being unskilled projects managers & the unproductive team [4]. Clinical data build the key evidence and conclusive results of any clinical trial. Therefore, data quality is key to successful study closure [5].

Multiple factors are associated with the failure of clinical trials. Patient recruitment and retention are affected

negatively when patients are concerned about being assigned to a control group rather than receiving an active study drug. Part of this effect may be due to patients having poor knowledge about placebos [6,7].

Poorly conducted studies, failure to interpret preclinical trial data and results of early phase 1 and 2b studies, do grossly effect the planning of the larger studies (Table 2) [8,9].

Factor	Association
Poor Study Design in Early & Late Phases of Clinical Trials	Inappropriate Eligibility Criteria
	Inadequate Literature Survey
	Inconsistencies in Protocol
	Sample size Errors—According to the NIH, More than 80% of clinical trials in the US fail to meet patient enrollment criteria.
	Improper dose selection
	Reducing Amendments
	Proper randomization and Blinding
Poor patient recruitment	25% of cancer trials failed to enroll a sufficient number of patients, and 18% of trials closed with less than half of the target.
Ineffective Site Selection	Overburdened Centre
ADR Monitoring	Inadequate Training & Regulatory Training

Table 2: Factors associated with Clinical Trial Failure.

The failure of trials will obviously impact the share value of the company which will fall drastically, once the drug is in the Phase III clinical trial (Table 3) [10]. The principal

investigator can and should challenge company in the initial stage if he is not confident about the outcome of the molecule (Table 4) [11].

Clinical Evaluation
Absence or insufficient demonstration of proof-of-concept in early trials
High false response rate in phase 2 trials
Uncertainties about the placebo response
Animal studies often do not correlate with clinical studies, due to the specie difference

Table 3: Why did some of the Trials, fail in Phase IIb and Phase III?

Patient Impact	Failed trials can worsen a patient's quality of life, emotional well-being, and prognosis
Financial impact on the company	Failed trials can result in significant financial losses for pharmaceutical companies, investors, and the economy
	Failed Phase 3 trials can threaten the survival of small biotech companies and investors. Even big pharma giants have lost significant fortune following drug withdrawal due to safety reasons. Troglitazone in 1998 by Glaxo and Cerivastatin by Bayer in 2001

Table 4: Consequences of Clinical Trial Failure.

Conclusion

Clinical trials involve significant investments of time and expenditure. 8-40 % of trials failed to recruit an adequate sample population in oncology. RCTs evaluating new anticancer agents fail more often than RCTs in other areas of medicine. There are various steps to reduce clinical trial failure they include identifying promising drug candidates (Biomarker testing can help identify efficacy or lack thereof, enabling pharma to identify promising drug candidates). Leveraging big data - enormous amounts of data over the years, is cumulated now the same is effectively using it. With advanced storage and machine learning, algorithms, analysis tools, and other technologies now available, one can begin to standardize, correlate, and leverage this data. Some trials do not go through the entire phase III evaluation due to cost constraints. 22% of the failed phase 3 studies failed due to lack of funding, as mentioned in the concluding statement by Fogel DB [1]. 63% of phase I oncology trials progress to phase II, but only 25% of phase II studies move on to phase III. This means only 15% of oncology studies in phase I will make it to phase 3. It's mandatory to have an Independent Data Monitoring Committee to maintain the integrity and the validity of clinical trials.

References

1. Fogel DB (2018) Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review, *Contemp Clin Trials Commun* 11: 156-164.
2. Sun D, Gao W, Hu H, Zhou S (2022) Why 90% of clinical drug development fails and how to improve it. *Acta Pharmaceutica Sinica B* 12(7): 3049-3062.
3. Hwang T, Carpenter D, Lauffenburger JC, Wang B, Franklin JM, et al. (2016) Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results. *JAMA Intern Med* 176(12): 1826-1833.
4. Stensland KD, DeParto K, Ryan J, Kaffenburger S, Reinstatler LS, et al. (2021) Estimating the Rate and Reasons of Clinical Trial Failure in Urologic Oncology. *Urol Oncol* 39(3): 154-160.
5. Zhang Z, Yin J, Yue Y, Su Y, Jiang H (2022) Assessing clinical trial failure risk factors and reasons in gastric cancer, *BMC Gastroenterology* 22(1): 496.
6. Gouin M, Auble H, Moreau P, Chevallier P, Peterlin P, et al. (2023) Unsupervised Analysis of Screen Failure Rates during Clinical Trial Enrollment Practice in a Tertiary Clinical Center of Hematology, *Clinics in Oncology* 8: 1-3.
7. Chow SC, Chow SS, Pong A (2021) Review of current controversial issues in clinical trials. *General Psychiatry* 34(5): e100540.
8. Buonansegna E, Salomo S, Maier AM, Li-Yang J (2014) Pharmaceutical new product development: Why do clinical trials fail. *R&D Management* 44(2): 189-202.
9. Ratziu V, Friedman SL (2023) Why Do So Many

Nonalcoholic Steatohepatitis Trials Fail. *Gastroenterology* 165: 5-10.

10. Harrison RK (2016) Phase II and phase III failures: 2013–2015. *Nature Reviews Drug Discovery* 15(12): 817-818.

11. Singh H, Sarangi SC, Gupta YK (2018) French Phase I Clinical Trial Disaster: Issues, Learning Points, and Potential Safety Measures. *Journal of Natural Science Biology and Medicine* 9(2): 106-110.