Paper TT01

Failed Clinical Trials: How to Benefit From Negative Experience

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ABSTRACT

Failed clinical trials can cost sponsors more than a billion dollars, and they can waste years developing a drug that will never reach the market. There are many ways for things to go wrong. These could include lack of efficacy, safety concerns, insufficient funding, or patient recruitment, enrollment, and retention. This paper analyzes various reasons behind failed clinical trials, including internal and external factors contributing to trial outcomes. Also, we would like to highlight indicators that predict potential study difficulties or even failure, and if the decision of study closure was made, what are the next steps from the patient and study management team perspective? Furthermore, this paper raises the question of whether some proactive strategies and best practices can help mitigate these risks and increase the likelihood of future trial success.

INTRODUCTION

Companies take on significant risks to bring life-saving medicines to market. According to the report 'Clinical Development Success Rates and Contributing Factors 2011–2020' from the Biotechnology Innovation Organization (BIO), the average likelihood of approval (LOA) from Phase I was 7.9%. This probability also depends on disease areas: the highest percent of success was in Hematology (23.9%), and the lowest in Urology (3.6%) [1]. The rate is even lower for significant disease categories, such as oncology (see Figure 1).

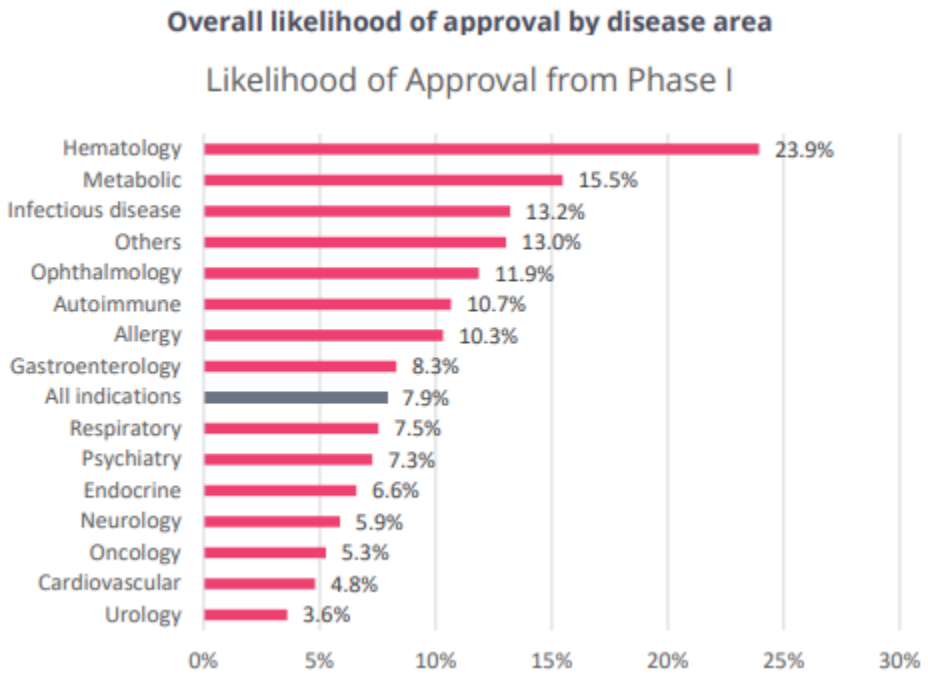

Figure 1: Chart of the likelihood of approval (LOA) from Phase I

On average, the full journey from Phase I to regulatory approval lasts 10.5 years. Among all the stages, Phase II development continues to present the most significant challenge in the drug development process, with just 28.9% of candidates achieving this critical phase transition (Figure 2).

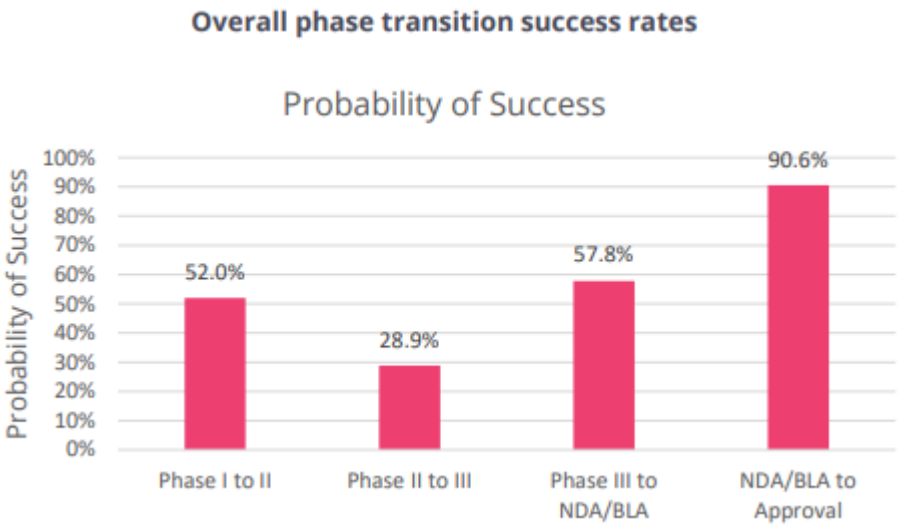

Figure 2: Phase transition success rates from Phase I for all diseases

The cost of failed clinical trials is extremely high - estimates vary, figures range from $800 million to $1.4 billion. According to an estimate from Deloitte (from 2023), the average cost of developing a candidate from discovery through clinical trials to the market is about $2.3 billion [2].

A failed trial often results in a decline in stock price for companies, the closure of research sites, and workforce reductions. This may even involve the sale of therapeutic areas to preserve the core business. This has an impact on employees and shareholders, but effects patients even more.

FACTORS IN CLINICAL TRIAL FAILURES

The drug development process generally follows a traditional sequence, encompassing a series of strict steps, including the validation of genetic and genomic targets, preclinical efficacy and toxicity testing, and the selection of patients and optimal clinical trial designs, often guided by biomarkers.

A review of clinical trials over the past few decades reveals that the 90% failure rate in drug development can be attributed to four primary factors: lack of clinical efficacy (40%–50%), unmanageable toxicity (30%), poor drug-like properties (10%–15%), and insufficient commercial viability and strategic planning (10%) that includes factors such as inadequate manufacturing protocols, operational issues, or challenges with patient recruitment, enrollment, and retention.

All factors contributing to the overall outcome can be categorized as internal or external. This section will examine each of these in closer detail [3].

INTERNAL FACTORS

1. Failing to demonstrate safety and efficacy: molecule doesn’t work

When we say the treatment or molecule doesn’t work, we mean that it doesn’t demonstrate expected efficacy or has unacceptable side effects or toxicity that outweigh its potential benefits.
Talking about toxicity, not only its magnitude but also its predictability is important. There are a few types of toxicity:

- severe and generalized;
- severe and unpredictable;
- other types, such as severe but predictable (for example toxicity after a certain cumulative dose or in patients with reduced renal function) can be designed around.

Potentially every molecule is toxic, hence the problem here is not the toxicity itself, but rather the unpredictable effects that lead to clinical trial failure [4, 5].

2. Poor drug-like properties

Drug-like properties frequently impact the drug's behavior within the body, creating obstacles during the development process. Poor drug-like properties include low solubility, rapid metabolism, unfavorable pharmacokinetics, chemical instability, difficulty in formulation, and others. These and other poor drug-like properties can cause a drug candidate to fail during the drug development process, especially in the stages when the drug is tested in humans.

3. Planning and operational issues

3.1 Study Design Flaws

Errors in clinical trial design are perhaps the most common reason trials fail, as are other planning and operational issues. There are many variables in clinical trial design but of those, four are the most important when it comes to ensuring a successful clinical trial: selecting the right sample size, the right patients, the right dosing, and the right endpoint.

Often, a drug has biological activity but it is tested for the wrong indication. Or, it is tested in the right indication but in the wrong subpopulations. In other instances, the wrong dose or dose interval is selected.

3.1.1 Right Endpoint

The first critical factor is the endpoint - the clinical or surrogate phenomenon that is assessed to determine whether the drug is effective.

One of the ways you can mis-design an endpoint is to include non-modifiable phenomena. One example was the pexelizumab (C5 inhibitor) study for bypass surgeries. The endpoint was myocardial infarctions (MI) and death. The level of troponin necessary to qualify as an MI was set quite low, presumably in an attempt to power the study adequately. The problem is that during a bypass, you almost always get a low level of troponin leak just from the surgical trauma to the heart. This non-modifiable low troponin elevation should have been excluded from the endpoint. Then the study would have been positive rather than negative [4].

Another way that an endpoint can fail is if it lacks responsiveness (i.e., sensitivity of the measure to actual changes in a phenomenon). For example, if the endpoint is remission, defined as a 30% improvement in symptoms, a drug that only improves symptoms by 10% will not generate a signal.

Related to responsiveness is a selection of the wrong statistical analysis. The analysis must match the type of disease and the response curve we expect to get. If we expect the drug to show an effect only after 3 months of treatment, we shouldn't use an analysis that examines the hazard ratio throughout the study.

In addition, the analysis methodology and the endpoint should be robust to dropouts and missing data. Patients may drop out of trials. Data may be lost. So we should have well-defined algorithms to interpolate the missing data.

One more way that a poor endpoint can lead to a negative trial is high variability. Ideally, repeated measurements for an endpoint should produce similar values but they often don't. Sometimes variability can't be avoided, but in other cases, the variability rises from rectifiable factors. For example, if you don't use a core lab for reading X-rays, you get inter-reader variability. If you don't use the same rater to rate joint swelling on every visit, you get inter-rater variability.

3.1.2 Right Dose

The second critical parameter in clinical study design is dosing. One of the most common errors in dose selection is simply selecting a dose that is too high or too low. Unfortunately, it often happens that the previous studies simply were not large or thorough enough to collect enough data to select the ideal dose.

A less common but still frequently seen error is using a dosing regimen that is too undifferentiated, such as a flat dose. When great heterogeneity in patient response or a narrow therapeutic window exists, you may have to customize the dose.

3.1.3 Right Patient

The third critical parameter in clinical study design is patient selection. An inappropriate population can lead to a negative study via a selection of patients who do not meet optimal inclusion/exclusion criteria.

3.1.4 Right Sample Size

And the last critical planning factor, contributing to clinical trial failure, is inadequate sample size.

- A smaller-than-required number of participants can undermine the statistical power of the study, hence reducing the probability that a trial will detect a true effect if it exists. Also, smaller trials are more susceptible to biases, for instance, the characteristics of participants (e.g., age, disease severity) might not be well-balanced between treatment groups. There is also a risk of not capturing enough data to identify less common adverse events or side effects, which could be significant when the drug is used in a larger population. As a result a promising treatment may be incorrectly deemed ineffective.
- The variability within the data may also be too high to draw reliable conclusions. This can make it difficult to determine whether observed effects are due to the treatment or just random chance. As a result, the trial might produce ambiguous or inconclusive results, preventing clear decisions about the drug's efficacy or safety.

Inadequate sample size may fail to meet regulatory standards, leading to difficulties in obtaining approval or requests for additional studies, which can delay or halt the drug development process.

3.2 Protocol deviations

Any deviations to the protocol-mandated procedures study must be identified, reviewed, and reported, and corrective and preventive actions as appropriate are taken to ensure patient safety and maintain data integrity.

Protocol deviations can impair the data quality and integrity, can affect the rights, safety, and welfare of the participants, and can undermine the scientific validity and reliability of the study data. Deviations are one of the most common causes of FDA inspection warning letters. Despite the increased focus on monitoring, audits, and regulatory inspections, protocol deviations remain a major challenge in the conduct of clinical studies.

3.3 Data quality

Clinical data are the foundation of any clinical trial, providing the key evidence and conclusive results upon which the trial's success is based. The absence of data quality monitoring during the study conduct period will have regrettable consequences. The introduction of noise due to miscalibration of measurement devices, or misunderstanding of measurement methods, for example, will negatively influence the resulting confidence intervals and subsequently the critical trial outcomes.

Some companies offer regular manual statistical quality checks of raw clinical data, while others provide statistical data surveillance services during a clinical trial. This preventive service acts as an "early smoke detector" in the study, preventing an actual fire from breaking out [3].

4. Sponsor-Related Issues

4.1 Financial Constraints

Restrictions on funding for a trial can result in compromises across various aspects of the study, including patient recruitment, site management, and data monitoring. Insufficient funding can lead to an underpowered study, delays, or even the inability to complete the trial, all of which can ultimately fail.

4.2 Strategic Decisions

Sponsors may decide to terminate a clinical trial early due to interim data that appears unfavorable, financial pressures, or strategic shifts within the company. While early termination can save resources, it can also lead to missed opportunities to gather valuable data that might have shown the treatment's benefits if the trial had continued.

On the other hand, sponsors may decide to continue clinical trials for the next phases despite the fact that the results of the previous one are not very promising. There is the case when Phase II results did not support the primary endpoint,

but the drug demonstrated potential. Rather than retesting the molecule, the developer initiated and ultimately concluded a Phase III program. The primary shareholder was focused on this single application, and the company subsequently filed for bankruptcy [6].

EXTERNAL FACTORS

External factors are often beyond the direct control of the trial sponsors and can include regulatory, environmental, societal, and logistical challenges. Here are some of them:

1. Regulatory Challenges

Regulatory requirements vary significantly across countries and regions. Delays in obtaining approval from regulatory authorities, changes in regulatory guidelines during the trial, or failure to meet regulatory standards can lead to trial delays, increased costs, or even termination, especially in multi-country trials.

2. Epidemics and Pandemics

Health crises such as pandemics can severely disrupt clinical trials. For example, the COVID-19 pandemic led to the suspension or delay of many trials due to lockdowns, reallocation of healthcare resources, and difficulties in accessing trial sites.

3. Geopolitical factors

Political instability, changes in government, international conflicts, or wars can disrupt clinical trials, especially in multinational studies. This may lead to site closures, difficulties in transporting materials, or challenges in coordinating trial activities across borders. Trade restrictions or sanctions can also limit access to necessary supplies or collaborators.

HIGH-RISK PROJECTS

It's also worth mentioning clinical trials that refer to studies that have a higher likelihood of encountering significant challenges or failing to achieve their intended outcomes. For instance, about 85 percent of central nervous system trials fail, compared to a failure rate of less than 70 percent in areas such as vaccine or ophthalmology trials. The biggest cause of CNS trial failure is the "placebo response". Subjects psychologically believe they are receiving benefits from the investigational drug even though they are unknowingly assigned to the trial's placebo arm. Many studies have suggested that placebo response rates are going up in neuroscience in general, the problem seems to be particularly pronounced in trials that look at pain and psychiatric medications.

A second, related problem is an over-reliance on subjective outcomes instead of more quantifiable biomarkers. For instance, the use of patient-reported outcomes (PROs) in clinical trials for central nervous system (CNS) conditions can present challenges due to the variability in how patients perceive and report their symptoms.

Another problem in CNS studies has to do with medication adherence. In pain studies, adherence rates can be as low as 50 percent. Medication adherence also is problematic in depression and other conditions that affect mood and behaviors. All of these problems make it less likely that a study will yield reliable, statistically significant results [7].

HOW TO RESCUE 'FAILED' CLINICAL TRIALS AND MINIMIZE RISKS

Lessons can be learned from both successful and unsuccessful clinical trials. The results of clinical trials are utilized by medical professionals, researchers, and patients to make well-informed decisions regarding treatment options.

1. Pharma companies don't share results (especially bad ones)

In 2007 Food and Drug Administration Amendments Act of 2007 (FDAAA, [8]) was signed, and among other regulations it requires certain clinical trials to report results [9]. After a long wait, it effectively came into force for all trials due after January 2018. According to the FDAAA Trials Tracker, only 77.4% of clinical trials were reported [10].

Everyone is anxious to publish positive trials—investigators, sponsors, and journals. However, trials with negative results are twice as likely to remain unreported as those with positive results [11]. The phenomenon is known as "publication bias," whereby only the positive results of studies are ultimately published. This indicates that patients and doctors don't have the full information regarding the advantages and disadvantages of specific treatments.

But knowing what failed can be as important as knowing what worked. Negative results can bring new insights into the safety and pharmacology of investigated agents. In the absence of awareness of safety and efficacy concerns and issues of failed drugs, researchers may persist in advancing investigational agents to clinical trials that are unlikely to demonstrate benefit. Consequently, future research subjects may be more vulnerable to potential risks associated with toxic or futile treatments [12].

In light of the rising costs associated with clinical trials, it is becoming increasingly clear that a lack of information sharing is a significant waste of resources and diverts attention from more productive areas of research.

2. Listen to the patient's story

Traditional trials often miss out on the patient's story. By listening to the narratives of patients you can pick up a deeper understanding of the needs and challenges that go beyond the simple presence of a side effect but are instead something that can impact their sleep, daily life, or mental well-being. Some of the advantages of this attitude is shown on Figure 3.

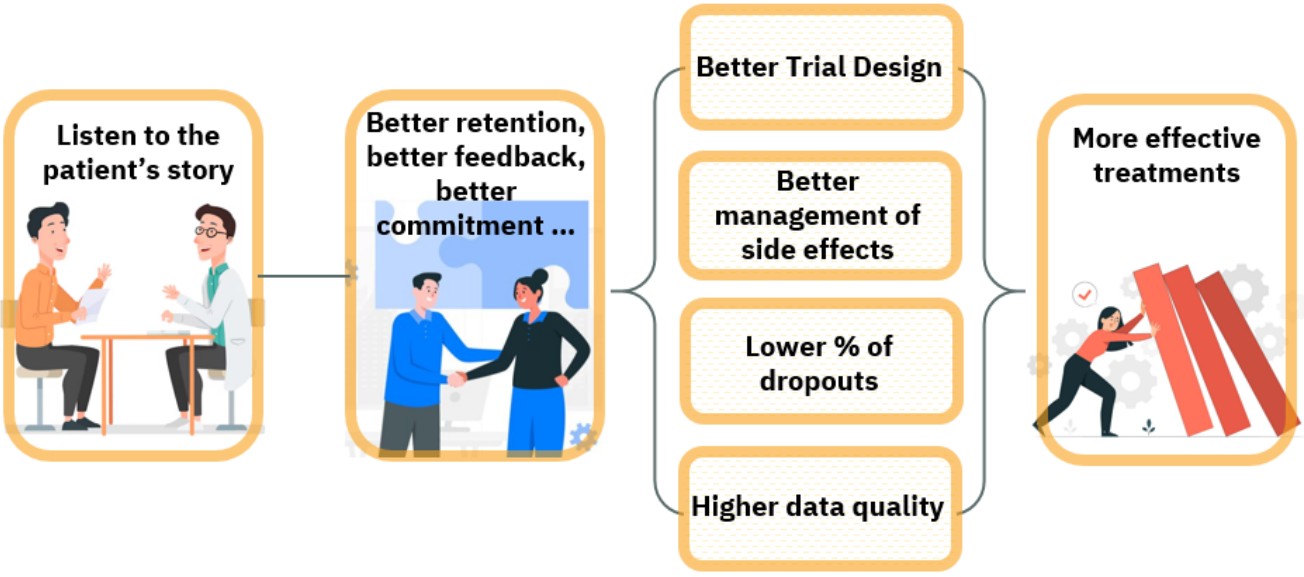

Figure 3: Advantages of Enhanced Patient Engagement

Involving patients as active participants fosters a sense of ownership and empowerment, leading to decreasing dropout rates and to more meaningful contributions in general [13].

3. Adaptive designs

Adaptive designs offer a more flexible approach to clinical trials, allowing trial results to be used to modify the trial's course following pre-specified rules. Adaptive designs provide a pathway to more efficient trials that are also more appealing from a patient's perspective in comparison to non-ADs as [14]:

- It may be necessary to terminate recruitment to futile treatment arms at an earlier stage;
- A smaller number of patients may be randomized to a less promising treatment or dose;
- On average, fewer patients may be required overall to ensure the same high level of statistical power;

- An underpowered trial, which would mean a waste of resources, may be prevented;
- A more precise understanding of the dose-response or dose–toxicity relationship may be achieved, thus facilitating the identification of a safe and effective dose for use in clinical practice;
- The patient population most likely to benefit from a treatment may be identified.
- A definitive conclusion can be reached earlier, so it will be possible to make new effective medicines available to a wider patient population who did not participate in the trial before.

Despite the clear benefits of ADs in many situations, they remain underutilized in practice, even though they have been available for more than 30 years. The lack of clarity about when adaptive designs are applicable, what they can (and cannot) accomplish, what their practical implications are, and how their results should be interpreted and reported are a significant challenge. There are some case studies, which show the benefits of adaptive designs [15]:

1) The Combination Assessment of Ranolazine in Stable Angina (CARISA). The sample size necessary to achieve 90% power was calculated as 462, and expanded to 577 to account for potential dropouts. After 231 patients had been randomized and followed up for 12 weeks, the investigators undertook a planned blinded sample size re-estimation. The standard deviation of the primary endpoint turned out to be considerably higher than planned for, so the recruitment target was increased by 40% to 810. The adaptation prevented an underpowered trial and the trial met the primary endpoint.
2) Telmisartan and Insulin Resistance in HIV (TAILoR). The interim analysis was conducted when results were available for half of the planned maximum of 336 patients. The two lowest dose arms were stopped for futility, whereas the 80 mg arm, which showed promising results at the interim, was continued along with the control.

ADs can bring about major benefits, such as shortening the trial duration or obtaining more precise conclusions, but typically at the price of being more complex than traditional fixed designs.

4. Using RWD (real-world data) and RWE (real-world evidence)

The growing accessibility of RWD (real-world data) and the rapid advancement of AI and ML techniques, coupled with rising costs and the acknowledged limitations of traditional trials, has driven significant interest in utilizing RWD to improve the efficiency of clinical research and discoveries and to bridge the evidence gap between clinical research and practice [16].

For example, during the COVID-19 pandemic, RWD were used to generate or aid the generation of real-world evidence (RWE) on the effectiveness of COVID-19 vaccination, and to characterize COVID-19 and flu using data from smartphones and wearables [17, 18, 19].

The main characteristic of RWD is that it is observational as opposed to data gathered in a controlled setting.

Due to the unique characteristics of RWD, there are a few key challenges that must be considered. These include the presence of unstructured, heterogeneous, incomplete, and inconsistent data; a high risk of bias and measurement errors; and the need for qualified staff, algorithms, and applications to process RWD.

Using and analyzing RWD

Talking about the use of RWD and RWE, it is worthy to mention pragmatic clinical trials that are designed to test the effectiveness of an intervention in the real-world clinical setting [20].

RWD also can be used in target trial emulation - the application of trial design and analysis principles from (target) randomized trials to the analysis of observational data. It may serve as an important tool especially when comparative evaluation is not yet available or feasible in randomized trials. Target trial emulation has been used to evaluate the effect of colon cancer screening on cancer incidence over eight years of follow-up, and the risk of urinary tract infection among diabetic patients [21,22].

RWD also provides a great opportunity to study rare events given the data voluminousness [23].

RWE will not replace the need for data from traditional trials; however, technologies supporting RWD are enabling far richer and more diverse information to be collected during drug development. The incorporation of technologies for RWD collection (e.g., wearables) and the use of RWE in drug development decision-making may also inspire innovation in clinical programs and trial designs.

5. AI-driven platforms

During clinical trials, an enormous amount of data has to be generated and requires detailed evaluation. Artificial intelligence (AI) undoubtedly plays an essential role in fetching accurate data in clinical trials [24, 25].

In spring 2023, the FDA published a discussion paper to address necessary considerations for using AI in clinical trials and drug development such as data quality, human-led government, and model development standards.

Applications of AI in Clinical Trials

Integration of AI could help researchers with a lot of aspects of clinical trials. Some examples of AI utilization are listed below [26]:

- AI in Clinical Trial Design. AI-driven analytical tools help in quick comparison between current and past results of clinical trials, support patient programs, and post-market surveillance, and have unparalleled potential to analyze, organize, or collect data generated during clinical trials;
- Site Selections. AI in clinical trials helps pharmaceutical companies identify sites and investigators that meet their criteria and collect evidence to meet regulatory standards;
- Patient Enrolment and Recruitment. In combination with big data AI helps to utilize the historical data to predict patient availability, can analyze many factors beyond demographics and health data, including socioeconomic status, culture, and location, thereby identifying the most suitable clinical trial participants.
- Identify underrepresented populations. Artificial intelligence (AI) can play a pivotal role in identifying underrepresented populations in clinical trials by rapidly analyzing copious amounts of existing healthcare data. This information can direct researchers to proactively target and engage specific demographics that may have been historically overlooked;
- Patient Medication Adherence, Monitoring and Retention. AI in clinical trials helps with patient medication monitoring and management by automating the capturing process. The combination of AI algorithms with wearable digital technologies offers the ability to gain real-time insights and continuously monitor patients. Furthermore, AI algorithms help to retrieve data regarding the effectiveness and safety of treatments while analyzing the risk of dropouts, which in turn enhances patient engagement and retention;
- Biosimulation. Biosimulation is the process of modeling biological systems and processes on a computer using mathematical techniques and can be used by researchers to conduct digital human tests and measure the human reaction to a medicinal chemical before it is tested on humans. The simulation generates predictions based on models and data using AI and machine learning, thereby facilitating the exploration of questions related to optimal dosing, medication interactions, and population-level efficacy;
- Enable real-time monitoring. The use of AI enables the real-time monitoring of trial participants via wearable devices and sensors. Furthermore, the evidence indicated that ML algorithms supported early detection and prognosis of disease, thereby improving overall trial success.

Though AI in clinical trials obtains enormous benefits, limitations such as the lack of standardization and data quality issues (that have a direct impact on the prediction's accuracy), also data security and privacy concerns still have to be addressed.

The adoption of AI in clinical trials by biopharma companies brings innovation to trial designs, effortlessly increasing the analysis of drug discovery data collected during clinical trials. According to Roots Analysis, the global AI in clinical trials market size is estimated to be worth $ 8.5 billion in 2035, growing at a CAGR (Compound annual growth rate) of 16% during the forecast period 2023-2035. But some limitations and points of concern are unavoidable and should be considered.

WHAT CAN PREDICT POTENTIAL STUDY DIFFICULTIES OR EVEN FAILURE?

One of the indicators that predict potential study failure is an interim analysis which is a pre-planned evaluation of the data collected in a clinical trial at one or more points before the trial is completed. This analysis helps determine whether the trial should continue as planned, be modified, or be stopped early.

There are four main purposes of Interim Analysis:

1. Safety Monitoring

An interim analysis incorporating a safety assessment is designed to assess whether there is evidence for increased risk of adverse events in intervention study arms relative to the SOC (Standard of Care) arm or historic data. If safety concerns are identified, a study could either temporarily pause enrollment while investigating the potential causal nature between intervention and adverse events or terminate the trial before full enrollment.

An IDMC (Independent Data Monitoring Committee), DMC (Data Monitoring Committee) or DSMB (Data Safety Monitoring Board) can play a pivotal role in the success of a clinical trial. The role of the IDMC is to guarantee the safety of trial participants and the integrity of the trial process. IDMCs are often implemented in trials with adaptive designs or interim analyses that might lead to study modifications [27].

2. Efficacy Evaluation

The term "interim analysis" is most often used in the context of early reviews of data that could potentially lead to the termination of a trial if the results indicate efficacy. Should there be a large enough signal early in the study suggesting the efficacy of one intervention arm over another, then it may be ethically imperative and most efficient to stop the study early. Stopping early and reporting on findings will allow for the investigational product to progress faster in the development process to reach the target clinical population sooner.

3. Futility Assessment

An interim analysis incorporating a futility assessment is designed to assess whether a trial is likely to meet its objectives if continued to completion. In a traditional randomized clinical trial designed to detect a clinically meaningful treatment effect, futility suggests that observing a statistically significant result at the end of the study is unlikely. Stopping a futile trial early can increase efficiencies from cost, resource, and participant burden perspectives. Given this reasoning, futility analyses are most appropriate in mid-late-phase studies enrolling larger sample sizes.

4. Sample Size Re-estimation

A study with an interim analysis to re-estimate sample size is designed to modify the planned sample size based on the accumulating data within the trial to account for any uncertainty when conducting power calculations during the initial planning of the study. Re-estimating a sample size at an interim stage can increase the likelihood of a successful trial but may result in a substantial increase in the needed sample size if the initial sample size assumptions are very different from what is observed.

HOW TO USE INFORMATION REGARDING THE FAILED TRIAL?

Although the study doesn’t seem promising or even failed, some steps could be taken to benefit from the negative experience.

1. Identifying the promising sub-populations

Within failed trials, there are often sub-populations of patients who respond well to the treatment and suffer no adverse events. However, due to the overall numbers not reaching the required threshold, the trial is often abandoned. This results in sponsors losing their investment and patients who could potentially benefit from life-saving treatments being denied these innovations.

The use of AI and machine learning tools allows for the rapid analysis of clinical data sets, enabling the identification of promising populations, and who are at risk of adverse events. Sponsors who can identify perspective sub-populations at an earlier stage can adapt the trial to focus on those patients and capture better primary and secondary endpoints. This increases safety and treatment outcomes through better trial design and can rescue promising trials that would otherwise be deemed failures.

Conversely, when data indicates that no population is experiencing meaningful outcomes, sponsors can save hundreds of millions of dollars by terminating unsuccessful trials earlier and redirecting resources to molecules with greater potential for return on investment [28].

2. Lessons learned

If the trial can't be salvaged, the data can still be useful for learning why the drug ultimately failed. Everything has rarely gone wrong in a trial, and learning those lessons can help new drugs succeed.

Sponsors may continue their research in a better manner by updating study designs using the inputs from the failed trials.

3. Drug repurposing

The repurposing of drugs has the potential to bring about significant advances in patient care and could facilitate the discovery of new mechanisms of action for old drugs and new classes of medicines [29].

A recent analysis revealed that 35% of the 'transformative' drugs approved by the US FDA were repurposed products. The repurposing of existing products and services is particularly beneficial in the context of rare or neglected diseases [30]. Many successes have been achieved, the foremost including sildenafil (Viagra) for erectile dysfunction and pulmonary hypertension and thalidomide for leprosy and multiple myeloma [31, 32].

The data from failed clinical trials is an essential component of the overall scientific knowledge base. While unsuccessful clinical trials may not lead to the approval of a particular treatment or intervention, the data generated during these trials is still valuable and can contribute to future research and understanding.

NEXT STEPS AFTER THE STUDY CLOSURE

1. Patients' feelings, reactions, and FAQs

When a trial ends early, many participants and study partners describe being plunged into uncertainty and having questions about “what comes next?” For individuals with serious diagnoses as well as for their study partners, having access to specialists and medical care through participation in a clinical trial can promote health and foster feelings of security and safety. For some of them, the trial may be a means of gaining access to health care or expertise that isn't otherwise available to them. Thus, the termination of a clinical trial may precipitate feelings of vulnerability for participants and their study partners.

Patients may have questions addressed to the study team such as:

- Why did the trial end?
- What were the results?
- What are the next steps for this treatment or intervention?
- Can you share my results?
- Which group was I in? Did I receive the study treatment? Was I in the control group?
- Can I still receive or continue to receive the study treatment even if the trial has ended?
- Were there side effects during the trial? If the answer is yes, what does that mean for me? Did I experience any side effects?
- Are there any other opportunities for me to participate in another trial?
- Where can I go for support? Can I talk with my doctor about the trial or is the information confidential?

Sponsors and investigators should be prepared to answer these questions to avoid patients feeling sad, disappointed, afraid, vulnerable, or worried about what will happen next [33].

2. Actions After Study Closure

When a clinical study ends, it's important to take several steps to ensure ethical responsibility, regulatory compliance, and proper handling of the data and resources involved. These steps are critical for patients and the study management team.

2.1 Patient

Patients should be told right away if a study is closing. If patients get an experimental treatment that is being stopped, ensure that they can still get medical care. This may mean moving them to standard care or finding another therapy. Patients should know what will happen with the data, how it will be used, and that their information will be kept safe. Even after the study ends, patients should be monitored for any delayed side effects. Follow-up visits or phone calls may be scheduled as needed. If the experimental treatment was helping some patients, alternative options should be discussed. In some cases, the investigational drug might be used safely.

2.2 Study Management Team

The FDA, EMA, and ethics committees must be informed when a study ends. A final report must also be sent to these authorities, explaining why the study was closed, what was done with the data, and any conclusions were made. All data collected up to the closure should be recorded, cleaned, and stored securely. This data could be useful for future research. Study documents should be archived according to GCP guidelines. Clinical sites should be closed in an orderly way. It's important to make sure that all the participants keep getting the care they need after the study ends. This may involve talking to healthcare providers to move patients to other treatments. It's also important to be open with patients, regulators, and stakeholders about why the study is ending.

CONCLUSIONS

Despite significant advancements in drug development, the high failure rate of clinical trials underscores the persistent challenges that the industry faces. Clinical trial failures can arise from a wide array of factors, broadly categorized as internal (related to drug properties, trial design, and sponsor decisions) and external (factors beyond the control of the sponsor, such as regulations or global events). The decision to terminate a clinical trial is never made lightly, but when such a step is necessary, it is crucial to manage both the patients and the study data with care to ensure ethical and scientific integrity. This paper highlights the importance of proactive strategies that can help mitigate the risks of program failure. They include technology-driven strategies or simple steps that seem obvious but are sometimes missed. By following best practices and learning from past experiences, sponsors and researchers can significantly increase the likelihood of future trial success, thereby ensuring that fewer promising drugs fail to reach the market due to preventable issues.

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