Decoding Phase II Clinical Trial Terminations

Why Phase II trials are terminated and what can be done to improve Phase II success rates - the most critical inflection point for clinical development

The biopharmaceutical industry spends in excess of US$100 billion annually on research and development (R&D)\(^1\). The cost of developing and launching a new drug can escalate into the hundreds of millions to billions of dollars (USD)\(^2\). These substantial investment costs may be used by manufacturers to justify high drug prices, leading to a vortex of scrutiny from the public, policymakers and stakeholders. Our goal was to determine what aspects of Phase II clinical development can be further improved by better understanding why Phase II trials are terminated. These insights may enable drug developers to dramatically improve the overall probability of success, reduce excessive R&D spend, bring new treatments to market faster and, perhaps, price new drugs lower for greater patient access.

We focused on conducting an in-depth analysis of Phase II clinical trials because this phase of development is the most critical inflection point for clinical development (go/no-go) decisions, testing for both safety and efficacy. Phase II trials have the lowest success rates, in terms of progressing to the next phase of development. Only thirty percent (30%) of Phase II trials successfully progress to Phase III and merely fifteen percent (15%) eventually progress to launch\(^3\). Phase II trials also represent the greatest volume of trials by phase (~50% of all interventional Phase I-III trials)\(^4\), and can cost anywhere from US$8 million to US$20 million per trial, with an average cost of US$14 million per trial\(^5\). Furthermore, positive results in Phase II have not always translated well into Phase III, as evidenced by 22 studies profiled by the United Stated Food and Drug Administration (FDA) as well as one pharmaceutical company’s own analysis\(^6\)\(^9\).
Our analysis included 444 Phase II clinical trials from the ClinicalTrials.gov database, using the following selection criteria:

- Study type: interventional studies
- Study results: studies with results
- Recruitment Status: terminated
- Updated: results last updated between 5/1/2016 and 5/1/2017 (preceding 12 months).

Table 1 below exhibits the breakout of these parameters.

![Table 1: Phase II clinical trial selection criteria](image)

These factors allowed us to: (1) concentrate on drugs in development, (2) clearly delineate why Phase II trials are terminated, and (3) establish confidence that the results reflect the most updated inputs from the sponsors.

Once the trials were extracted and aggregated, we annotated the reported reasons for termination, and then categorized them into themes based on the following rationale:

1. Accrual – trials that stated low enrollment / accrual was the major causative factor
2. Strategy – trials that indicated business reasons, competitive environment, re-prioritization
3. Efficacy – trials that stated failure to meet endpoints, meeting futility analyses criteria
4. Safety – trials that stated dosing, equivalence, adverse events, tolerability as issues
5. Funding – trials that stated funding, either delayed or retracted, as the major reason
6. PI / Staff – trials that indicating either Principal Investigator (PI) and/or staff dispersed
7. Supply – trials that indicated shortage of drug supply or other supply chain issue
8. Regulatory – trials that indicated intervention by either the FDA or review boards (IRB)
9. Completed – trials stating completed, and terminated
The results of the analysis were then further dissected to compare and contrast termination rates and reasons across individual therapeutic areas (TA). The TAs reviewed included: Oncology, Neurology, Pulmonary, Inflammatory, Cardiovascular, Infectious Disease, Hepatology, Diabetes, Immune, and Endocrinology. We also segmented the results based on the funding source, classified either as Industry or Non-Industry sponsored, to determine whether there are differences in termination reasons between the two categories. For all Industry sponsored trials, we identified the lead company sponsors to establish a breakout by company.

The prevailing hypothesis, and ensuing claims, industry-wide, is that Phase II trials fail primarily because of safety or efficacy reasons.\textsuperscript{8,9} We found that the majority of Phase II trials were terminated due to Accrual (45%) and Strategy (20%) reasons, whereas Efficacy and Safety combined for only 20% of the reasons for termination (see Figure 1, above). It is also important to note that the termination themes are not all mutually exclusive. For instance, when accrual is the stated reason for termination, it may be due to a poor recruitment and retention ‘strategy’ and/or poor execution of the recruiting and retention process.

When comparing the source of funding for Phase II trials we found further differences in the reasons for termination. Accrual-related reasons accounted for 53% of terminations in non-Industry funded trials, as compared to 38% of Industry funded. Accrual and Strategy together accounted for nearly two-thirds of reasons in both categories of funding (see Figure 2, left).

These themes are also consistent over a time horizon. When segmenting the trials by First Received date, we find that Accrual and Strategy are the two main reasons for termination during an 11 year horizon, from 2005-2015 (see Figure 3, below).
When analyzing by TA, the data is significantly skewed towards Oncology, which comprises 65% of the trials analyzed. Figure 4 (below) shows the top 10 TAs and their termination reasons. Accrual is the reason for termination in more than 50% of Oncology trials and as high as 80% for Infectious Diseases. Strategy accounts for termination between 9% and 33% across the Top 10 TAs.

When analyzing the termination reasons for the studies funded by industry, we found that, on average, accrual and strategy accounted for approximately 38% and 22%, respectively, of terminated Phase II trials (see Figure 5, below). The results for the top five pharma companies
are presented for industry average comparisons. In all five companies, accrual and strategy reasons ranged from 40% to 70% of studies reported.

**Discussion**

There is little that can be done in terms of predicting or optimizing efficacy and safety, as evidenced when a trial fails in larger safety studies and/or efficacy for the first time. We do note that ‘failure’ can mean futility at the clinical level (i.e. failing to meet safety / efficacy endpoints), as well as terminated due to the reasons presented thus far (i.e. Accrual, Strategy etc.).

We posit that all other Phase II trial factors (i.e. Accrual, Strategy, Funding, PI/Staff, and Supply) can be optimized. For Accrual, there are multiple ways and rationale to positively impact patient enrollment and retention through improved strategies and operations \(^{10,11,12}\). It is estimated that only 2%-3% of total Phase II trial costs are devoted to patient recruitment and retention costs\(^5\). Why do sponsoring entities spend such significant capital on the overall conduct of (Phase II) clinical trials, yet exhibit such nominal spending on the critical components of recruitment and retention?

Strategy and Funding account for 25% of Phase II terminations. Strategic decisions, driven by unbiased and holistic evidence-based strategies should be performed often and iteratively. As Phase I trials are usually 12-18 months in duration, there is ample time to optimally evaluate and constantly re-evaluate clinical, competitive and commercial landscapes well ahead of entering Phase II trials, as well as during Phase II trial execution. Are drug developers using holistic data sets and encompassing all perceived stakeholder expectations when designing Phase II asset strategies?
1. **Conduct unbiased, introspective reviews to gain a comprehensive understanding of trial successes and failures; continuations and terminations**

The majority of published accounts point to Safety or Efficacy as the primary reasons for Phase II failure. Given the analysis and rationale above, we believe sponsor organizations ought to realize they need to move in a different direction; a direction that will enable them to improve Phase II results by focusing on developing and deploying targeted strategies directed at the specific reasons their Phase II trials are terminated. A comprehensive and unbiased analysis of clinical programs is likely not conducted at each company. Conducting a holistic analysis supplemented with context and input from key stakeholders is a logical first step. We further believe there needs to be greater transparency in strategic and operational activities conducted by partner organizations (i.e. contract research organizations (CROs), especially those activities related to clinical and commercial feasibility analysis.

2. **Understand that patient centricity needs to be more than a trendy term**

The recent paradigm shift to patient centricity may seem perplexing, to say the least. It almost seems that an interest in what matters to the patient is a novel and unique revelation. It’s critical for sponsor organizations to take a true account of patient needs, up-front and specific to each trial, and expend the necessary resources to address them. Even more staggering are site enrollment statistics: a 2013 study revealed half of all sites under-enroll, and timelines are doubled to meet enrollment targets\(^\text{13}\). If sponsors wish to develop and execute on strategies that can vastly improve recruitment and retention, they need to recognize and be sensitive to patient socio-economic burdens, thoughts on care options and interactions with trial coordinators. Treat the patient holistically and challenge recruitment and retention projections with vigor; don’t accept the status-quo.

3. **Evaluate and constantly re-evaluate strategies to improve the probability of success**

Sponsors can spend over US$1 billion 10 years developing a drug that fails\(^2\). At the onset of these efforts and during the 10-year time horizon, many sponsors expend little effort and capital on designing and redesigning unbiased evidence-driven Phase II development strategies. Sponsors typically use a small data set to help establish an initial strategy that, in many instances, is doomed to fail from the start. Vigilance in assessing payer/physician/payer needs; changing regulatory/reimbursement landscape; Phase III expectations; decisions related to divesting/developing/co-marketing assets can all pay significant dividends in designing and executing iterative clinical development strategies. These strategies should be designed to include such trends as patient insights, physician willingness to prescribe, payer willingness to place on formulary, etc. Whether the sponsor is an established company or a clinical-stage start-up, there are a multitude of reasons that could negatively affect an asset’s value potential that have very little to do with demonstrating superior clinical profiles.
As the old adage goes: it’s not what you can make, but what you can sell... executing flawed drug development strategies well isn’t the answer.

To have a deeper conversation about improving Phase II success rates and overall pipeline productivity, please contact:

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