

# Patient Recruitment Driving Length and Cost of Oncology Clinical Trials



**As prospective oncology drugs progress from Phase I to Phase III clinical trials, the difference between projected and actual patient enrolment durations typically increases. In most cases, oncology clinical trial delays are a direct result of patient recruitment challenges. This is particularly true when multiple companies run competing clinical trials, an increasingly common situation. Oncology research is the most active therapeutic area, with 10,303 drug programmes in process, accounting for 18% of all development programmes, according to BioPharm Insight.**

Cutting Edge Information's study, "Oncology Clinical Trials: Drug Development Resources and Case Studies," found that across all phases of oncology clinical trials, the two main factors impacting duration are the level of difficulty of trial-specific patient recruitment and the number of patient visits required by a trial.

Patient recruitment difficulties have become widespread as companies struggle to meet their trial enrolment targets. If a particular therapeutic area is already competitive, with a number of companies performing similar clinical trials, enrolling patients becomes even more challenging. Depending on how competitive a specific indication is, many potential patients may already be participating in other investigative trials. In regions with more available treatment options, patients may favour current standard of care regimens above investigative trials. Patient recruitment may be less challenging in regions where clinical trials may represent one of only a few cost-efficient treatment options available for patients.

## Average Trial Duration by Phase

Phase I trials averaged a 7.8-month delay between projected and actual end dates. Phase II trials reported an average of a 5.1-month delays and Phase III reported 6.4-month delays. Companies may have

a harder time developing participant criteria during Phase I — which explains patient recruitment difficulties present during some of the Phase I trials that Cutting Edge Information studied. By the time a compound enters Phase II investigative trials, companies have better refined and streamlined their enrolment criteria.

The number of patient visits required by investigative trials also influences the duration of profiled trials across Phases I, II and III. For trials requiring multiple patient visits, the amount of time trial participants must wait before undergoing additional monitored visits may skew the actual trial duration.

## Increased Duration, Increased Cost

Clinical development groups continue to dedicate the considerable resources necessary to bring investigational treatments to market — and considerable may be an understatement. Based on the trial data that Cutting Edge Information collected, advancing an oncology treatment through Phase I, Phase II and Phase III clinical trials costs a combined average of \$56.3 million and eight years. These data do not include time spent in pre-clinical testing and regulatory filing that add to both development cost and time.

On the surface, Phase III trials are much more expensive than Phase II trials. In one study, the average total cost for Phase III trials (\$41.7 million) stood four times higher than the average cost for Phase II trials (\$10.2 million). But much of those cost differences are the result of the larger patient enrolment required during Phase III. On a per-patient basis, Phase III trials cost only 7% more than Phase II trials, according to interviews for a recent benchmarking study.

As oncology products successfully progress through each stage of clinical development, the stakes grow higher and higher. Theoretically, a drug failure in late-stage trials is exponentially more costly than an early-stage failure. The pharmaceutical company not only loses the monetary investment made in clinical research, but also the opportunity to invest in other pipeline candidates.

## Significant Variation Across Indications

During Phase I and Phase II trials, oncology clinical trial durations average 27.5 and 26.1 months, respectively. The longest trial durations during these phases fall between 48 and 50 months. By comparison, the average length of a Phase III trial, according to surveyed trial



profiles, is approximately 41 months; the longest Phase III trial topped 81 months.

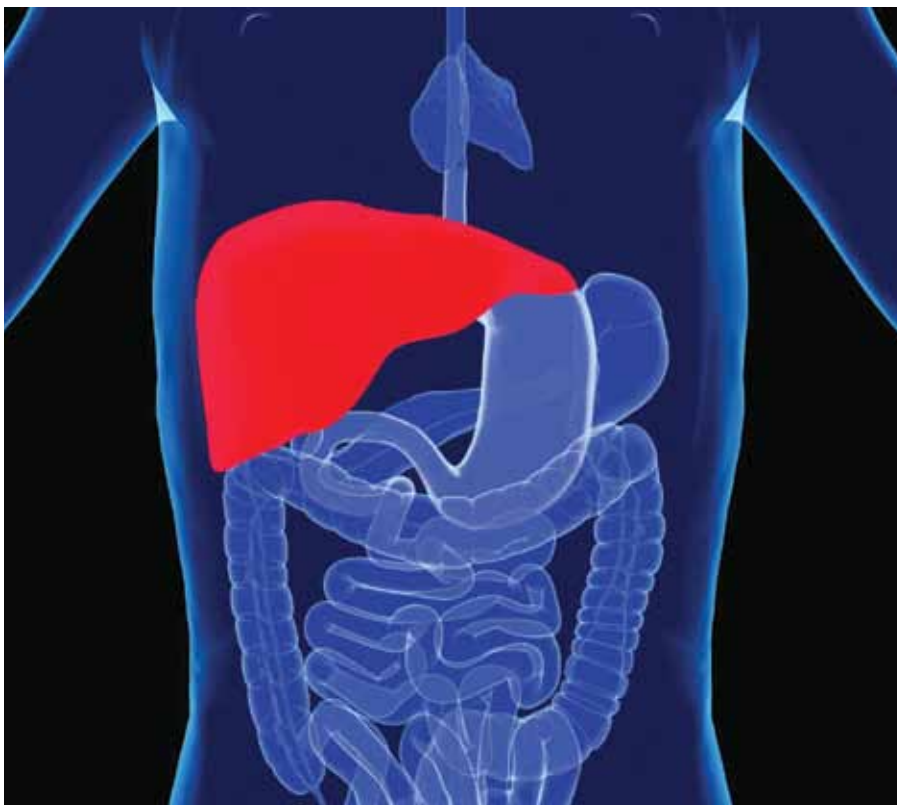
More common diseases such as breast cancer and prostate cancer have been studied extensively and the pharmaceutical industry has made significant breakthroughs, including 188 and 99 approved treatments in both indications, respectively.

Developing treatments for other types of cancer has proven more challenging — particularly liver cancer and melanoma, which only have 11 and 15 approved treatments respectively. But the pharmaceutical industry seems up to the challenge with a host of promising drug programmes being tested in those areas of critical need. Melanoma has 158 active drug programmes in either Phase II or Phase III testing, while liver cancer has 92 drug programmes in late-stage testing. Another highly active area of oncology research is solid tumours, with 845 active drug programmes.

The total cost of an oncology trial varies greatly depending on the specific indication, required medical procedures in the protocol, and location. One Phase III trial reported a total cost of \$88 million, while another Phase III trial reported a cost of only \$3.4 million. The most obvious factor that sets these two trials apart was a difference in patient enrolment of approximately 700 patients. The number of patients enrolled is the greatest driver of overall trial cost, according to Cutting Edge Information's study. To more accurately compare the 29 oncology trials examined in this report, analysts relied heavily on metrics such as per-patient trial costs, patients per clinical research associate, and patients per site.

### Patient Recruitment Challenges

Oncology clinical trials' patient recruitment difficulties are not caused by a lack of patients. The US National Cancer Institute estimated that, in 2012, there were 1.6 million newly diagnosed cancer cases and a total of 577,000 cancer deaths in the United States alone. These numbers grow several times higher when the rest of the world is included. Incidence rates of prostate cancer in US men have risen to 1.4 for every 1000; a commonly held theory asserts that one out of every nine women will develop breast cancer at some point in their lives. Patient recruitment goals are achievable



because the disease state is so prevalent: 1,756 solid tumour trials were registered in the United States from 2003 to 2012.

Depending on the specific area of oncology being studied, some targeted patients may already be participating in other clinical trials. In the areas where there are more available treatment options, patients may prefer the current standard of care as opposed to unproven investigative clinical trials. Cutting Edge Information found that drug companies can lessen the patient recruitment challenge in geographic areas where clinical trials are one of the few low-cost treatment options available for afflicted patients.

Patient recruitment is easier for Phase I oncology trials because trial protocols generally require fewer patients, and the combination of cancer patients and healthy volunteers makes recruitment easier, yet. Phase II and Phase III trials have much smaller patient groups at each investigator site. The requirement of patients with a very specific disease state slows patient recruitment, causing trial managers to depend on more sites to reach enrolment targets. Although average overall enrolment is much greater for these later-phase trials, enrolment is spread over many more sites.

The ratio of patients to investigator sites is a revealing metric in comparing

trial phases. Cutting Edge Information's research shows a strong correlation between number of patients and number of sites (correlation coefficient = 0.85). Fewer sites with larger patient groups are characteristic of Phase I trials while Phase II and Phase III trials tend to have more sites with fewer patients at each. These metrics are useful to trial managers deciding how many sites a trial will need to reach the target patient enrolment.

### Patient Recruitment Strategies

Working in the healthcare industry's favour is that patients' altruistic feelings drive many of them to participate in clinical studies. One company surveyed by Cutting Edge Information conducted a survey of its patients and found that 90% of patients who have participated in clinical trials would do so again. The challenge is to gain access to these willing participants. To do this, it is crucial that trial sponsors diligently evaluate sites and build strong relationships with high-performing investigators. Using CROs or large networks of clinical trial sites can open the door to the desired patient populations.

Performing patient demographic research can aid in site selection and protocol design, ensuring the best chance for recruitment success. Evaluating patient populations can both pinpoint

geographic concentrations of disease and improve the diversity of trial sites to better meet regulators' requirements. Other market research can allow a trial manager to accurately identify which motivators will work most effectively; for example, what might motivate a senior citizen is likely not the same for a 19-year-old. Likewise, different reimbursement and communication tools may motivate patients in densely populated areas and rural settings.

A keen understanding of patient demographics can aid trial protocol designers in both motivating participation and improving retention. One successful strategy is to design trials that will make participation easier and more convenient, such as requiring fewer return visits and allowing for some treatment follow-up by phone. These techniques are simple and inexpensive to implement, and they protect the study from losing its most valuable asset: patients.

Nevertheless, patient recruitment strategies and motivators also present challenges. Successful patient recruitment requires an investment of time and money that many drug companies rarely consider when setting a study budget. To save money, sponsors may choose to skip important aspects of the recruitment process, including patient demographic research. The same occurs with patient retention strategies; once patients are recruited, study sponsors may think the job is complete. But extra investment during the patient recruitment and retention phases rewards forward-thinking trial managers. Taking adequate time to evaluate sites and spending money on additional tools will speed patient recruitment, eliminate delays, help to meet target enrolment and, in many cases, save money.

### Other Cost-saving Strategies

In an effort to save money, many companies have turned to contract research organisations (CROs) for a large portion of their clinical trial activities. But these cost-savings occur because CROs have developed highly efficient clinical operations. CROs have collected performance measurements on clinical trial operations for years, and the drug companies have caught on. Now the average clinical trial tracks 14.6 performance metrics. Along with these rising costs, companies are increasing

the percentage of their clinical budgets allocated to outsourced organisations. One contributing factor is a move toward more full-service clinical vendors. Full-service vendors allow companies to minimise internal FTE contribution and avoid over-resourcing during clinical downtimes. Despite the trend of increased outsourcing, companies have found ways to limit outsourcing while continuing to reap the benefits by building internal CROs.

Another solution that several drug companies at the forefront of clinical efficiency have explored is adaptive clinical trial design. Adaptive design allows clinical teams to adjust the parameters of a trial midstream, shifting patients and resources to treatment arms with greater probability of success. Although the concept of adaptive design has been around in different forms for several years, an FDA guidance set forth in 2010 finally addressed some of the life science industry's key questions on the topic. Despite the guidance, drug companies' apprehensions remain, preventing the industry from widespread adoption of this efficient clinical technique.

A more widespread adoption of adaptive design into clinical trials is held up by three main obstacles: statistical challenges, operational challenges and executive-level acceptance. The statistical and operational challenges can be solved with rapidly advancing technologies that allow clinicians to avoid introducing bias into their studies. Finding acceptance, however, is still a work in progress.

Adaptive design is a marked departure from the tried-and-true clinical trial design, leaving pharma executives cautious about implementing it into expensive and critically important late-stage trials. Instead, pharma is more comfortable applying adaptive design to early-stage trials, where companies can more easily mitigate risks. The FDA's guidance provided a loose framework within which late-stage registration trials could successfully use adaptive design. But until some high-profile, successful registrations occur, the industry will continue to be lukewarm to the practice. Many clinical development groups still suspect that the FDA, despite its encouragement, is less likely to approve a drug studied under an adaptive design protocol.

There is, however, strong incentive for pharma to expand the use of adaptive design in all phases. When implemented properly, adaptive design offers many advantages. It can cut down trial costs by helping investigators realise that a drug will likely be unsuccessful, allowing the decision to terminate trials early. It can also get drugs to market faster, extending the critical time a drug has to generate revenue. Adaptive trial design allows investigators to make important adjustments to an ongoing trial that could improve the trial's probability of success and/or approval. But the scope — and indeed the very existence of these advantages — depend on numerous variables.

The one consistent, reliable advantage offered by adaptive design is saving time. By allowing investigators to make better choices about treatment arms, dosage levels and sample size, adaptive design can bring a trial to conclusion several months earlier than a traditional trial design would allow for. Even if the company terminates the trial early, the sponsor is still saving time that would have otherwise been wasted on an unsuccessful endeavour. The time saved can be significant; survey respondents reported saving as much as one year on trial duration through the use of adaptive design.

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