TAKING THE GUESSWORK OUT OF FEASIBILITY ASSESSMENT IN ONCOLOGY TRIALS

Data Drives Greater Predictability, Speed and Savings for Sponsors

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The scientific progress being made in cancer research has never been more encouraging or more rewarding. Yet, virtually all oncology drug sponsors face an uphill battle in what one would expect to be the easiest part of the research process: recruiting patients for clinical trials. Despite the seriousness of the diagnosis—or perhaps because of it—only three percent of adult patients with cancer participate in clinical trials.[1] As a result, under-enrollment is common.

If patient enrollment is difficult, forecasting patient enrollment is even more so. In general, the methods that sponsors use to forecast enrollment in any therapeutic area aren't very accurate. Across the board, nearly 80 percent of clinical trials fail to meet their enrollment timelines.[2] And, nearly a third (30 percent) of Phase III study terminations are due to enrollment difficulties,[3] making recruitment the single biggest reason for trial failure. Many of these failures can be traced back to some combination of poor planning and insufficient monitoring once recruitment is underway.

Sponsors who wish for greater trial predictability, shorter timelines and meaningful cost savings must assure that their forecasts are realistic and achievable. Doing so is possible by combining data and sophisticated informatics tools to evaluate the feasibility of a sponsor's intentions and timelines. And this can be done with a high degree of precision, as outlined below.

THE RECRUITMENT CHALLENGE BEHIND THE PLANNING CHALLENGE

Before we explore the mechanics of the enrollment forecasting process, it's worth reviewing why patient recruitment—especially for oncology trials—is so very challenging. Several basic factors about the market and the nature of the disease itself inhibit ready access to patients for trials. These include:

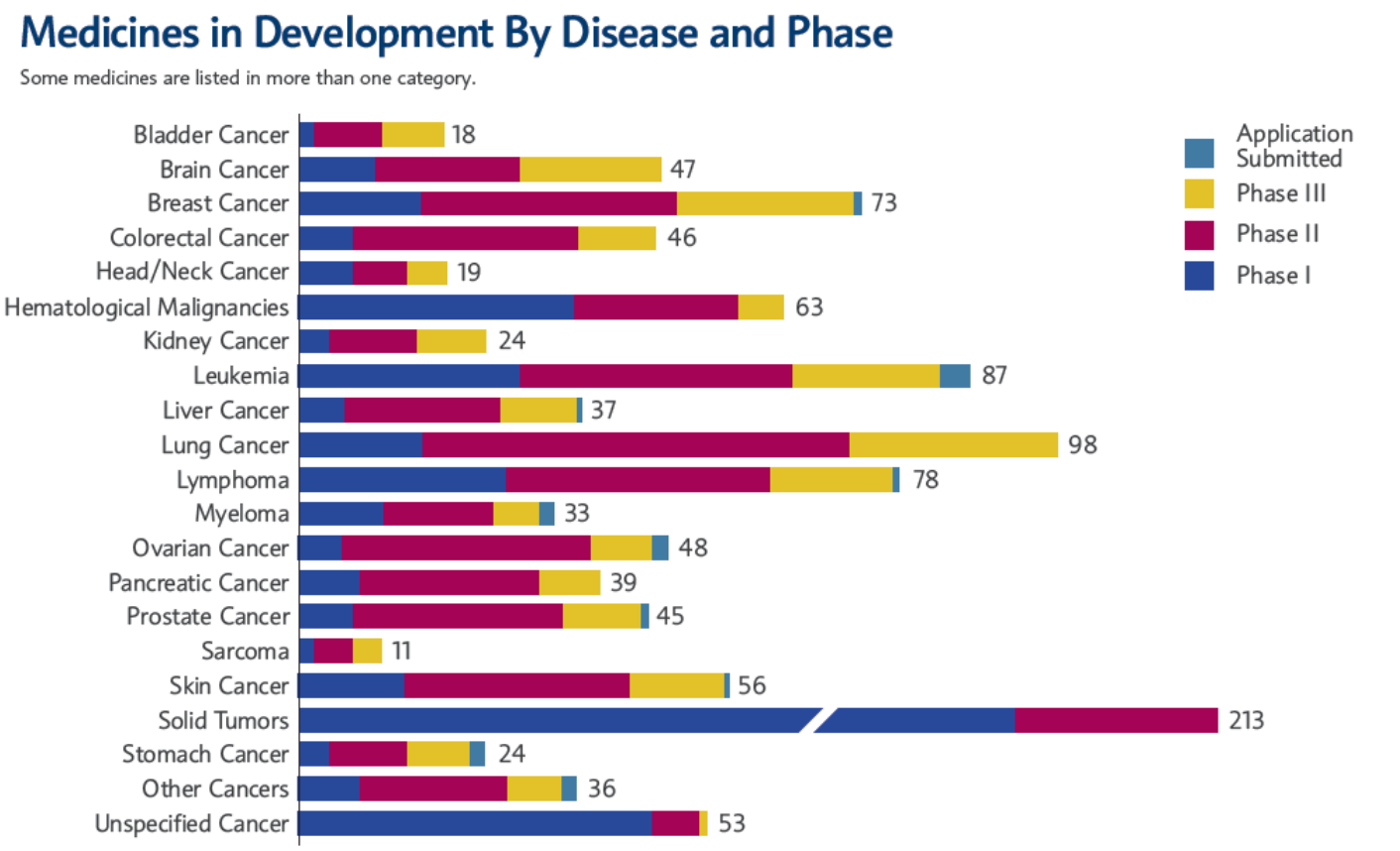
- **Heavy competition.** In most tumor areas, there is heavy competition for patients, as can be inferred from Figure 1. The National Cancer Institute reports that there are currently 12,000+ oncology clinical trials now accepting patients. Another 25,000 trials in progress are no longer accepting patients, having already drawn from the finite pool of potential participants.

  Competition is most intense within the large, academic medical centers where key opinion leaders practice. Still, these saturated facilities remain the sites of choice for most sponsors.

- **Reliance on investigators.** The nature of the disease is usually not conducive to traditional direct-to-patient recruitment tactics, so sponsors must rely to a large extent on investigators to identify suitable patients. To be effective, investigators must identify trial candidates based on very specific inclusion/exclusion criteria and they must do so while likely recruiting candidates for multiple trials (given the competition mentioned above) and balancing other clinical and non-clinical responsibilities. This is often a tall order.

Figure 1: Medicines in Development by Disease and Phase

(Source: PhRMA at http://www.phrma.org/sites/default/files/pdf/2014-cancer-report.pdf)



- **The severity of the diagnosis.** Faced with a cancer diagnosis, most patients want access to the standard of care in the early stages of disease. Only when first line therapy fails, do many patients become more interested in participating in a trial for an experimental treatment. By this time, they may have received chemotherapy, some types of which are often excluded in oncology trials, making it difficult to find suitable patients.
- **Other patient fears/concerns.** These include concerns over quality of life and possible side effects, as well as a fear of receiving a placebo.[4]
- **Logistics and burden on caretakers.** In some cases, patients are reluctant to participate in clinical trials because of the extra burden it would place on family members/caretakers in accommodating a more rigorous treatment regimen.

THE FORECASTING CHALLENGE

Often, under-enrollment in trials is the result of overestimating what can be achieved rather than of not delivering on what is possible. Forecasts that sponsors create as part of their trial plans are frequently based on incorrect assumptions and are overly optimistic.

Trial planners are unusually hampered in oncology trials for three primary reasons: the "snowflake effect," oncology criteria and the oncology-specific pacing of enrollment.

The snowflake effect comes into play because rarely are two oncology trials alike. This lack of true comparability between trials means that it is often difficult to use statistics from one trial to make decisions on another—for example about country selection or the number of sites required. Extrapolating performance data, such as site and screen

failure rates, from one oncology trial and applying it to another involves subjective judgment about the applicability of the reference trial.

The second and related issue is that enrollment projections must take into account a number of very specific criteria for any given oncology trial. These include the stage of the disease, the patient's prior lines of therapy, any required biomarkers for genotyping and the patient's performance status. Of these, the line of therapy and biomarker requirements are the most difficult to assess using traditional trial and site intelligence databases. For example, a review of a few oncology protocols recently evaluated revealed that triple negative breast cancer patients and notch +/- status can have significant effect on the feasibility of enrolling on time. Although each disease area has a set of specific requirements, oncology trials tend to be more difficult to assess for these reasons.

Finally, oncology trials often require that enrollment of one patient cohort be completed before moving on to the next. After the first cohort is enrolled, data may need to be analyzed to inform decisions on subsequent cohorts, such as dose selection and sample size. These interim analyses introduce delays, the length of which is hard to predict.

PROJECTING ENROLLMENT: THE LONG-ESTABLISHED APPROACH

The traditional approach to assessing recruitment feasibility is to survey investigative sites on their projected enrollment capability. Sponsors ask investigators to complete questionnaires on the number of patients in their practice who fit the study criteria and on how many they believe they can recruit for an upcoming trial.

This step is certainly worthwhile, particularly when the information gathered is combined with other information. One caveat, however, is that most oncologists do not actually run queries against a patient database to answer the first question with precision; they simply provide a rough estimate of their current patient population. Nor can they divine the future. Again, they make an educated guess as to how many patients they hope to furnish. Patient counts gathered directly from investigators should be taken for what they are: a best guesstimate provided by a busy professional eager to do the best thing for patients.

Tempering investigators' feedback with their own experience and intuition, sponsors then arrive at a mean or median enrollment rate that suggests the number of patients they might expect per site, per week. Using a basic Excel spreadsheet, they create a linear projection of how quickly sites will enroll patients. But this antiquated, deterministic approach to enrollment projection does not always account for all of the differences in recruiting capability from one site to the next, or one country to another.

> *"Patient counts gathered directly from investigators should be taken for what they are: a best guesstimate provided by a busy professional eager to do the best thing for patients."*

This approach produces results that are mixed at best. Sponsors need a better, more reliable and more sophisticated way to estimate recruitment rates and quantify timeline risk.

A RECOMMENDED APPROACH FOR PROJECTING ENROLLMENT FOR PHASE II/III TRIALS

Today, there are many rich sources of data that can inform the trial forecast, as well as advanced statistical tools to test various "what if" scenarios and establish confidence levels in the results. It is possible for sponsors to begin their recruitment based on a sound plan, rather than guesswork. They can proceed with a high degree of confidence that they can meet their enrollment targets, on time and on budget. A best-practice approach incorporates information gleaned from physician surveys and combines it with the experienced judgment of study planners before integrating it into a much more comprehensive, data-driven analysis of enrollment potential.

The result is a far more accurate baseline forecast that predicts the probability of enrollment success within a specific timeframe and given certain variables. This is a more comprehensive, stochastic approach to enrollment modeling—an approach that factors in multiple inputs and key enrollment considerations.

Let's walk through the process, step by step.

1) The first step is to create a preliminary, rough country and site selection strategy.

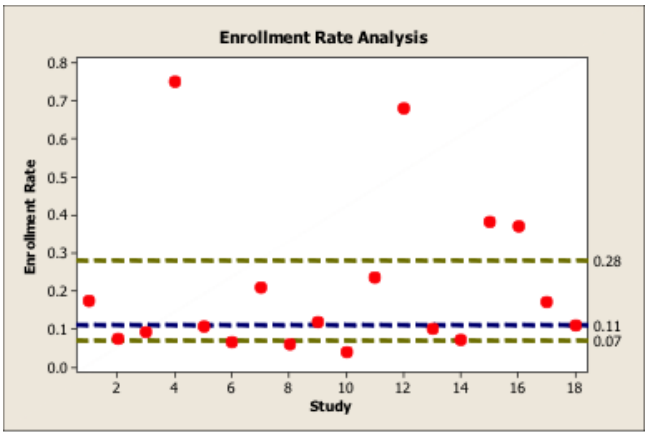
- Draw upon a variety of clinical trial intelligence databases to score and rank countries according to key selection parameters, such as relevant trial experience in specific trials, the competitive environment, investigator access potential, incidence or prevalence and study initiation timeline.

2) Next, estimate the enrollment timeline.

- Study historical enrollment rates from previous clinical trials that are analogous to the trial at hand, considering the indication, stage of the disease, line of therapy, genotyping and epidemiology by country and region. Given the unique nature of each oncology protocol, it is not always possible to find a good historical match, so this step often requires subjective judgment in how the trial in question will compare to previous ones.

  In any case, it is good practice to describe enrollment trends seen in closely matched trials to understand historical performance. Figure 2 is a plot of sample enrollment trends showing enrollment rates for 19 comparable trials that ranged from a 25th percentile of 0.7 patients per site per month (p/s/m) to a 75th percentile of 0.28 p/s/m. The median enrollment rate was 0.11 p/s/m and a mean of 0.21 p/s/m.

Figure 2: Historical Enrollment Rates in Comparable Studies



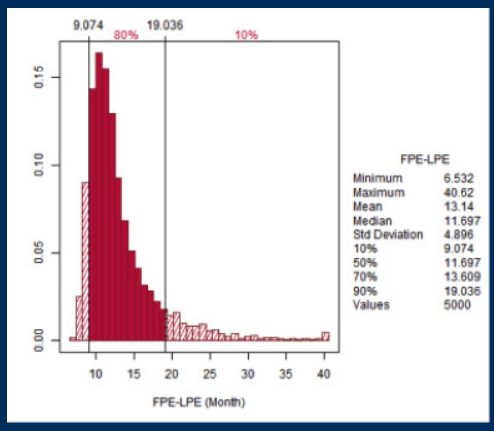
A Case in Point

One sponsor conducting an ongoing Phase III trial in mesothelioma had an unexpected change in the trial's scope: the enrollment target of 180 patients was increased to 564. Eighty-four patients had been enrolled, so another 480 were needed. The study team, concerned about the likelihood of completing enrollment on time, requested a feasibility assessment using enrollment modeling.

Monte Carlo Simulation technology was used in a stochastic model not only to project the time to complete enrollment, but also to provide a probability of success in achieving the projected timeline. The analysis combined data on the actual screen failure and enrollment rates from sites that were already enrolling and estimated start dates for others.

The model ran 5,000 simulations to project an enrollment duration of 13.6 months, with a 70 percent probability of success, an acceptable level of risk in clinical trial planning. (See Fig. 4.)

Figure 4: Projected Enrollment Period Distribution Curve for Mesothelioma Study



In fact, the study was enrolled in 12 months, about 1.5 months ahead of the projection. The speedier enrollment was attributed to the investigational drug's great appeal as a novel agent with great potential. Statisticians noted the enrollment rate trending high during the first few months of the study, but kept the projection conservative to reflect what is typically seen in oncology trials. The approach proved to be an effective and valuable tool to the study team for whom closing the study early was a welcome outcome.

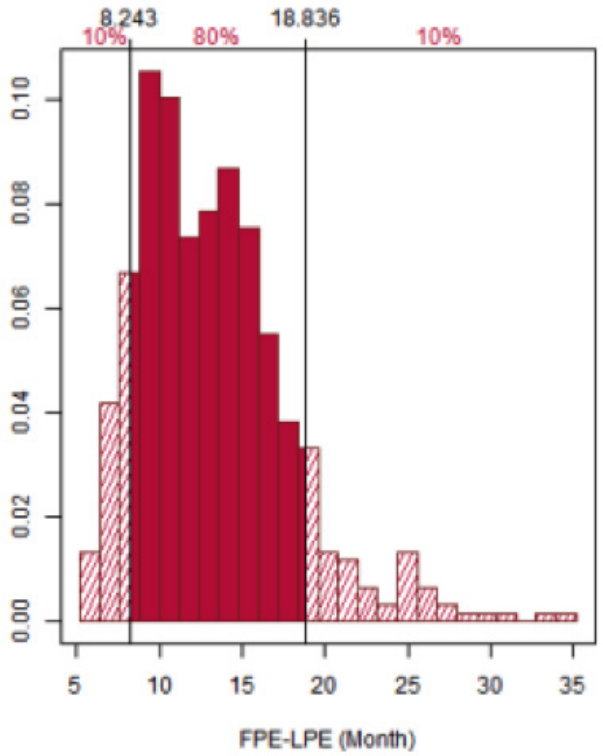
- The results of the above research can be loaded into a statistical model designed to forecast enrollment rates based on different variables. The specific statistical technique, Monte Carlo Simulation (MCS), calculates the probability that a particular outcome will occur based on a given set of assumptions. It works by assigning a range of values to each input variable, such as country distribution, recruitment rate patient availability, number of sites, site activation time and screen failure ratio. Given the higher degree of uncertainty in oncology trials, the ranges within these parameters are generally wider than in other therapeutic areas.

The software then runs a series of virtual trial simulations —between 1,000 and 5,000—each with a different set of random values from within the range. In enrollment forecasting, the output can be displayed as a distribution chart showing the probability of meeting enrollment targets for each scenario.

This modeling technique gives a sponsor a quantifiable measure of risk related to whether a particular country and site mix will be able to enroll the target number of patients by a specific deadline.

Figure 3 is a sample enrollment period distribution chart, the main output of the MCS. The chart shows that this particular study has only a 10 percent probability of completing enrollment in the eight months desired by the sponsor. Without the appropriate tools to flag significant enrollment risks, this study and others like it would go into rescue mode. The trial sponsor would need to add new, unplanned countries and sites, initiate costly advertising or undertake other patient recruitment remediation campaigns. The bottom line: costly delays.

Figure 3: Enrollment Period Distribution Curve



3) The third step in the process is to develop a refined list of potential investigative sites.

- To develop a list of potential investigators, review numerous, dynamic investigator databases containing published performance metrics on study start up, enrollment, quality of data and any specific protocol considerations.

- Mine health insurance databases and other types of electronic health information, as appropriate, to determine disease prevalence estimates, support site selection and assess enrollment potential.

- Survey sites to gauge their interest and suitability via a questionnaire that considers access to patients, standard of care, familiarity with the patient evaluation criteria, available staff and resources and investigator experience.

- Create a decision support tool that weights each survey response according to its importance in site selection. Assign an overall score to each site, and then rank them against each another.

The data-driven approach described here is thorough, but does not take long to complete if the necessary data sources are already identified and the analytical steps and statistical methodologies pre-established. It is possible to conduct the necessary research and analysis to prepare a baseline enrollment forecast in only a few days. This small investment in creating a better plan pays dividends in helping study managers maintain control of the recruitment process and avoid the turmoil and added expense of switching into "rescue mode."

CONCLUSION

Too many sponsors know firsthand the downside of over estimating how quickly an oncology trial can be enrolled. From the operational costs of rescuing or extending a trial to the lost opportunity cost of delayed market entry, the financial ramifications can be astronomical.

The solution lies in combining data and appropriate expertise with sophisticated informatics tools to evaluate the feasibility of an enrollment timeline with precision. By taking such a data-driven approach, sponsors can begin their oncology trials with more realistic expectations—both in terms of budgets and timelines—and with greater predictability in planning.

REFERENCES

1. Institute of Medicine Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington, DC: National Academies Press; 2010.
2. Hess, Jon, "Web-Based Patient Recruitment," Cutting Edge information, http://www.cuttingedgeinfo.com/process/?ref=122
3. Li, Gen, PhD, MBA and Gray, Robert, MBA, "Performance-Based Site Selection Reduces Costs and Shortens Enrollment Time," Monitor, December 2011. Based on analysis of 5,000 terminated clinical trials.
4. Mills EJ, et al. "Barriers to participation in clinical trials of cancer: A meta-analysis and systematic review of patient-reported factors." Lancet Oncology. 2006; 7(2):141–148.

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