Predictive Modeling in Clinical Trial Enrollment

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Predictive modeling plays a critical role in successful clinical trial recruitment planning and completion. Using predictive modeling, clinical study teams can estimate the time needed to recruit the required number of enrolled subjects using a set number of sites. Additionally, modeling provides a plan for the study team to measure enrollment progress as the study advances. Needless to say, a recruitment plan is only helpful if it is reliable and accurate; otherwise, the study team may be trying to adhere to an unrealistic, potentially overly optimistic, plan.

Most sponsors use trend analysis to predict enrollment. On day one, a projection is created assuming an equal number of patients will enroll each month. As recruitment progresses, the trial managers rely on matching the actual performance to the straight-line projection. If the actual performance diverges from the expected performance, the expected line is adjusted accordingly.

Acurian takes a different approach to predictive modeling, building its own model from the ground up using proprietary enrollment metrics from over 400 trials. Acurian's predictive enrollment model provides more realistic and accurate recruitment plans than traditional trend analysis methodologies.

The Two Components behind Predictive Enrollment Modeling

Two components must be estimated in a predictive enrollment model regardless of the model and its calculation method: patient yield and recruitment timeline. The patient yield estimates the final number of enrolled patients given the indication, inclusion/exclusion criteria, and how many people in the general population will be messaged to for the clinical study. The recruitment timeline estimates the length of time to recruit a certain number of patients.

Patient Yield

No two clinical trials are the same. One tiny difference in protocol requirements between two trials can cause drastic differences in achieving recruitment and enrollment timing. For this reason, every protocol needs to be uniquely assessed in order to estimate the patient yield. Many factors should be considered, such as inclusion/exclusion criteria, patient motivation, recruitment tactics, placebo allotment, development phase, and visit schedule. All of these items and more have an impact on the final number of patients who enroll in the trial.

Traditional trend analysis relies on a feasibility survey sent to the sites to estimate the patient yield. This method depends on the sites to provide accurate information on the number of patients they can enroll in the trial. More often than not, the sites are optimistic and overestimate the number of patients they can contribute. This inaccuracy occurs because the sites do not perform any kind of statistical analysis to estimate patient yield and they do not identify potential challenges that will limit their enrollment yield. Instead, they make subjective estimates on the number of patients they are able to provide.

It is important to be able to quantify specific protocol requirement challenges. For example, finding a migraine patient who has 3-8 migraines per month is 34% more difficult than finding a patient who has 2-8 migraines per month. There is no easy way to quantify these minute differences without having access to historical data.

Using Acurian's proprietary recruitment performance database of over 1,000,000 screened patients from actual trials, Acurian can objectively estimate the probability of a patient enrolling in a trial. Instead of using subjective methods and guesswork to estimate the effects of protocol requirements, Acurian's model is able to specify the exact impact of certain protocol requirements. Acurian's database can quantify exactly how many migraine patients attend their first office visit; exactly how many Type II diabetics are taking Metformin mono-therapy; and exactly how many Alzheimer's caregivers respond to a television advertisement versus a letter. The historical database applies known probabilities to a protocol's requirements, defining the patient yield with a high level of statistical confidence.

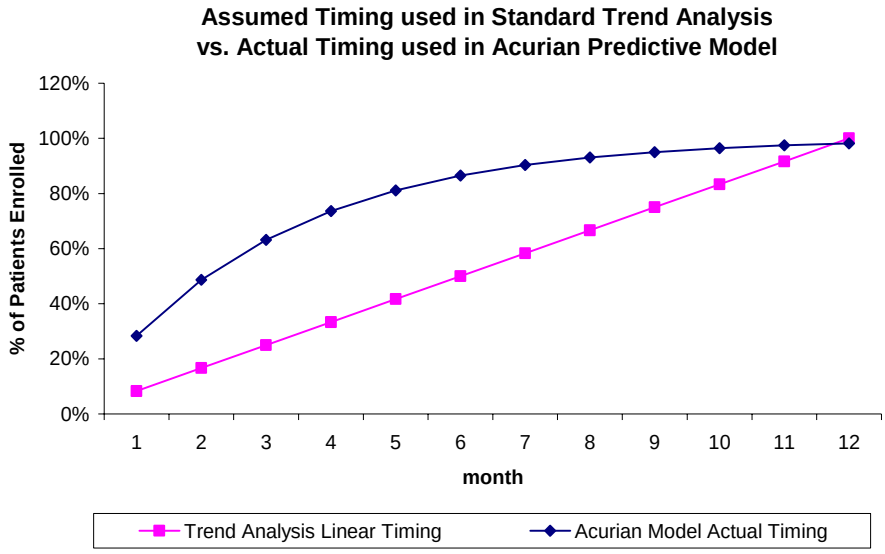
Recruitment Timeline

Estimating the number of enrolled patients only solves one piece of the puzzle. The second and equally critical piece is the length of time to recruit the needed number of patients. Further, a precise method to predict enrollment timing enables identification of study obstacles and unforeseen challenges very early in the study's life. Capturing issues and resolving them early in the recruitment process is the key to successfully completing enrollment on time.

Because timing is such an integral component of a predictive model, it is important to calculate this piece with a high degree of confidence. Traditional trend analysis assumes that patients enroll in a trial in a linear fashion. In other words, an equal number of patients will enroll per month. The linear timing assumption is used as a "best guess" only because no knowledge on actual timing behavior is known.

The data from over 400 real trials in Acurian's proprietary enrollment database enabled Acurian to measure the actual timing behavior seen in clinical trials. Contrary to popular industry practice, the timing equation does not follow a straight line, but follows the behavior illustrated in Figure 1.

Figure 1



As the graph shows, the timing behavior of patients enrolling in a trial does not follow a straight line.

Using Predictive Modeling to Expedite Enrollment

A particular model's level of success can be determined by how effectively it expedites enrollment. The most common method used by sponsors, trend analysis, does not expedite enrollment.

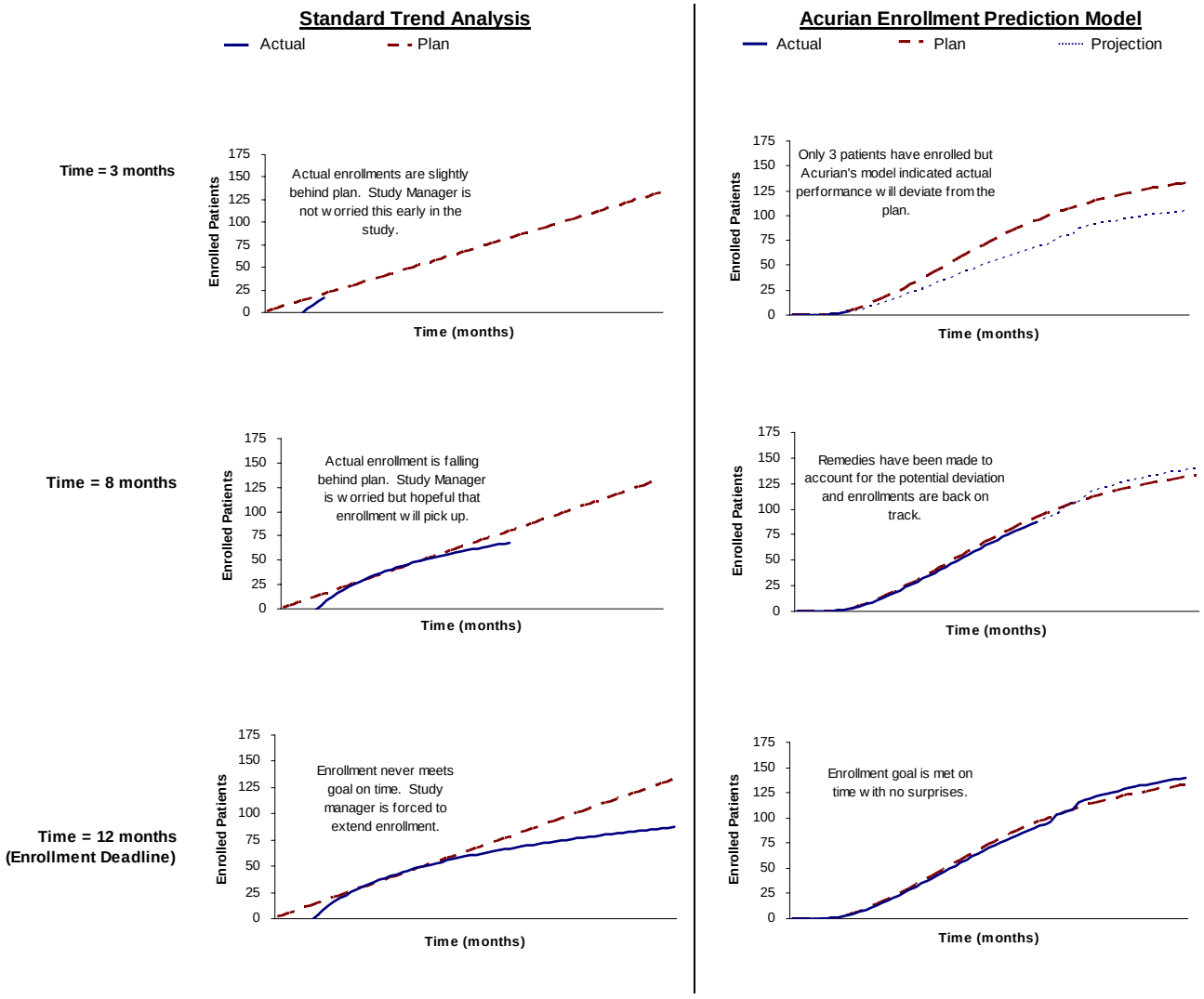
First, trend analysis relies on actual performance to make its prediction. As recruitment progresses, the trial managers adjust the straight-line projection based on the actual performance as it progresses. By the time the trial accrues enough randomizations to alert that the plan is off track, it is too late to recover the original enrollment timeline. Furthermore, spotting a divergence from the straight-line projection does not provide any new intelligence about the project to help it finish successfully. The divergence is simply a realization that the study is behind.

Second, trend analysis is not backed by real performance, but rather by a flawed timing equation and a subjective-based patient yield estimate. Therefore, the study team bases its recruitment plan on estimates that are overly optimistic, if possible at all.

Contrary to trend analysis where recruitment obstacles are revealed after they occur, Acurian's predictive model identifies potential challenges up front, preventing them from transpiring in the first place. Because Acurian's predictive model alerts the study manager of deviations from the plan before they occur, the study manager and recruitment vendor have the opportunity to adjust recruitment efforts so that enrollment never falls off track. With Acurian's predictive model, there is a realistic plan based on historical performance from studies done at the start of the trial.

Figure 2 demonstrates the progression of a trial using both trend analysis and Acurian's predictive enrollment model.

Figure 2



The example in Figure 2 shows that using the trend analysis method does not expedite enrollment. In fact it has caused the sponsor to extend the enrollment timeline. If trend analysis is used on the extended timeline, there is no telling when the study will end as it may go on for months and months before the sponsor is able to fill the enrollment gap.

On the contrary, Acurian's predictive enrollment model enabled the study to complete on time as planned. Since its prediction is based on historical trials' actual performances, the original plan was more realistic and easier to stay on track during the study.

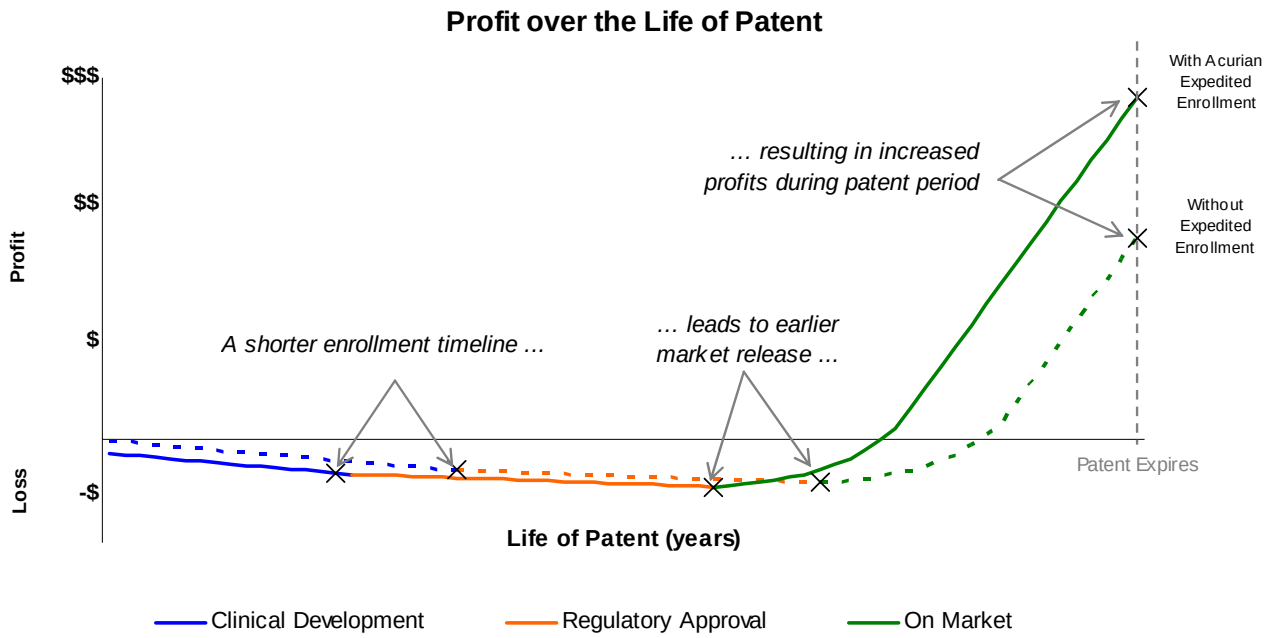
How Expedited Enrollment Saves Money

Enrollment is expedited using Acurian's predictive enrollment model. But what does expediting enrollment mean for the sponsor? Put simply, the more months saved in enrollment, the more money in the sponsor's pocket.

Cutting Edge, an industry publication, estimates that the average operating cost per patient for a phase II trial is $19,300 and for a phase III trial is $26,000. For illustration purposes, assume a phase III trial needs 2,000 patients and 24 months to complete enrollment. This translates to $2,166,667 of monthly operating costs (2,000 patients at $26,000 each is a total of $52,000,000 across 24 months). If Acurian's predictive model is employed to run this trial and the trial ends three months early, that translates to a direct savings of $6,500,000. The amount of direct savings varies depending on the trial specifics. But the bottom line is that any number of months saved in enrollment translates to direct savings in operating costs. Since operating costs can be significant, the monthly savings are usually substantial.

Besides direct savings on operating costs, expedited enrollment leads to increased revenue once the product goes to market. The patent life on a product is finite; therefore, the sponsor only has a set amount of time to develop the drug, test it, and bring it to market. The longer the sponsor takes developing and testing the drug in the clinical research phase, the less time the product is in the market earning money under an exclusive patent. By enrolling patients faster, Acurian's predictive enrollment model helps bring a product to the market faster, giving the sponsor more time to earn revenue on the product, without competition from generics. See Figure 3.

Figure 3



Summary

Acurian's predictive model more accurately determines timeframe and financial enrollment expectations than the more commonly used trend analysis. The predictive enrollment model paints a more accurate picture of what to expect when enrolling for a trial, because it is statistically backed by real data from real trials. The model provides quantitative estimates of patient feasibility and the actual timing behavior, translating to a more realistic plan that identifies potential issues while there is still time to course correct. A direct result of determining enrollment expectations is expedited study completion. A study using Acurian's predictive model completes on time if not earlier, meaning, for the sponsor, direct savings in operational costs and an increase in sales profit when the drug goes to market.

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