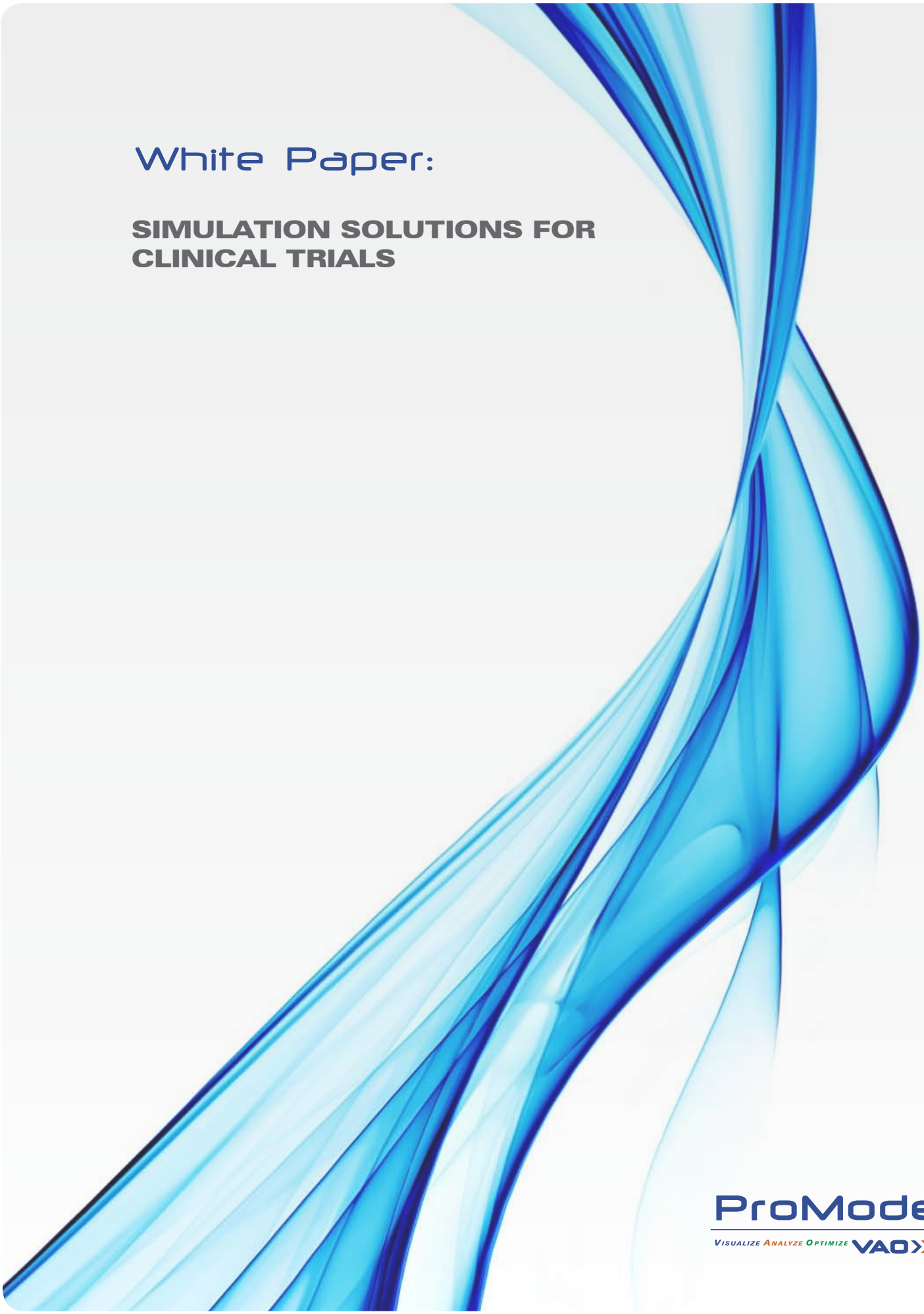
White Paper:

SIMULATION SOLUTIONS FOR CLINICAL TRIALS



ProModel

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SIMULATION SOLUTIONS FOR CLINICAL TRIALS

THE RISK WITH CLINICAL TRIALS

Clinical studies account for almost half of the over one billion dollar cost of drug development. According to separate studies conducted by McKinsey Quarterly and IBM Global Industries, more than 80% of all clinical trials experience significant delays costing pharmaceutical companies upwards of $35,000 a day per trial. Patient recruitment and retention are widely recognized as the leading bottleneck in the new drug development pipeline. In fact, just getting patients and dosage into clinical trials has become the most delayed ridden aspect of drug discovery and development over the past 10 years. The unfortunate result of this problem is that pharmaceutical, biotech, and medical device companies lose millions in additional development costs, and hundreds of millions in revenue simply because they have no way to clear this bottleneck.

Most large pharmaceutical firms conduct numerous clinical trials per year, and each must follow a specific protocol in order to carefully safeguard the health of the participants as well as answer specific research questions concerning: the type of people who may participate in the trial; the schedule of tests, procedures, medications, and dosages; as well as the length of each study. Due to these strict requirements, trial managers are under enormous pressure to more reliably predict site and patient recruitment, reduce the risk around projecting study milestones fulfillment and completion, and preemptively select the right sites for conducting their trials.

DYNAMIC DECISION SUPPORT FOR CLINICAL TRIALS

In order to effectively meet these requirements and continue to stay within budget, pharmaceutical companies are increasingly turning to simulation--a merger of strategy, analysis and technology that enables them to run through virtual scenarios of their major initiatives.

This type of powerful decision support technology can run multiple replications of many different scenarios that take into account the clinical trial process's variability and complex resource interdependence. These scenarios generate realistic data on how a company's patient recruitment process will perform. This includes enrolling recruiting sites, setting up training sites, getting patients recruited, dosing them, seeing them through the entire cycle, and then closing out the trial.

In short, using simulation technology in clinical trial patient enrollment enables managers to capture test center variability in a single cohesive summary. This brings a single flexible tool to companies that can track and address any situation that arises in the organization, granting greater visibility over the entire project life cycle.

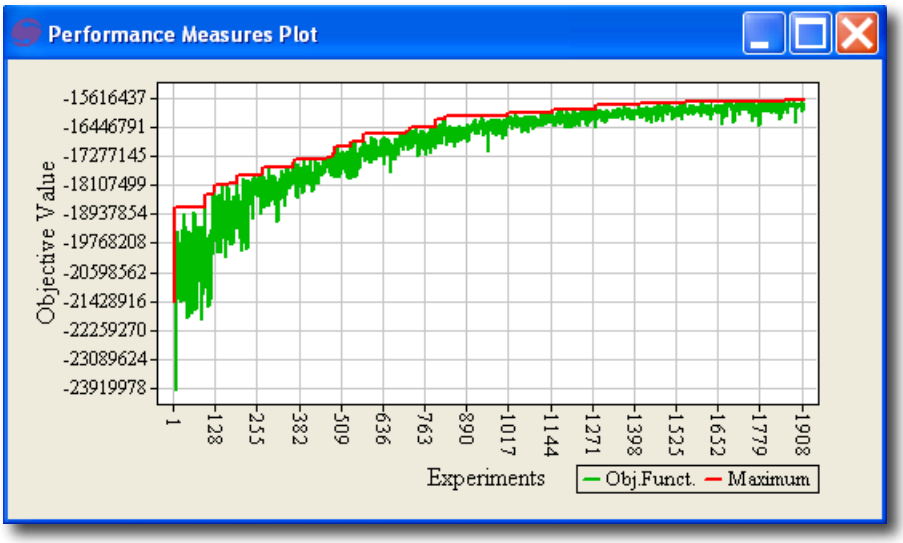
PROMODEL'S CLINICAL TRIALS SIMULATOR

ProModel offers such technology with Clinical Trials Simulator (CTS), a user friendly decision support technology that takes into account all the inherent variability in Clinical Trials and generates realistic data on how patient recruitment will perform which allows companies to make better decisions, faster. CTS allows you to mitigate the risk around recruitment by accurately projecting "true" patient enrollment and retention, which in turns enables precision forecasting when it comes to the optimal trial solution. This solution can be used in conjunction with existing or expected recruitment data to help predict how patient recruitment sites will perform based upon a predetermined protocol using a set of input templates. CTS can also facilitate cost avoidance, where companies can recognize a project's viability early in the process. If it won't be economically feasible to reach the patient recruitment goals in any realistic time frame, management can sunset the project, and save valuable resources.

Using simulation technology like Clinical Trials Simulator can provide an early indication of when and where trials are derailed. This awareness can be combined with additional simulation scenarios to quickly identify options to help the trial recover and complete its objectives with a minimal disturbance to the original targets. Plus, the program's results help trial managers produce more realistic, accurate goals. This makes the trial's management case much stronger before senior executives, and increases the chance the trial will receive support.

HOW SIMULATION WORKS

Simulation will provide the maximum value in cases where there is a choice regarding the selection of the trial site enrollment. Simulation can aid in identifying the group of sites which will best achieve the trial objectives for patient enrollment using both the trial completion date and the trial cost as the objective functions of the optimization process. Once the enrolling sites have been chosen and the trial is underway, this tool can continue to provide value by combining actual and projected patient enrollment to ensure that the projected schedule is met or exceeded. If problems occur and result in patient enrollment falling below expectations, simulation can aid in minimizing its impact on the overall trial. The comparison between actual and projected enrollment will not only make it possible to identify problems at an early stage, but it also can be used to evaluate the best option for recovering from the problem by evaluating whether it would be helpful to supplement the original list of enrolling sites.



The green plot records the result of each optimizer-controlled experiment as it continues to improve the best case output of the objective functions; minimizing both project cost and completion date.

IMPLEMENTING DECISION SUPPORT WITH SIMULATION

To begin using simulation technology for clinical trials, the first and most important step in the process is the collection of all data that will be entered into the system for analysis. Companies and their consultants or technology providers must review the available portfolio data and determine how long a particular site takes to get up to speed, when it's fully trained, when it starts enrolling patients, and what delays could arise.

Many times individual sites have their own data, or the pharmaceutical company has collected data from past experiences. Relevant information includes site type, delays to recruitment of the site, delays to training of the site, different cycle times, and more. The accuracy of the data regarding delays to site qualification and rate of patient enrollment is critical to the success of the trial. The risks of using data which is based on estimates rather than actual results can be mitigated by expanding the bounds of the distributions which are used for these entries in the simulation.

If a company and site have no data of their own, consultants will create a template of similar sites in the same country, and give it a suitable range of variability to accommodate margin of error. Both approaches share the same goal: to ensure data is accurate and dynamic, so companies can arrive at realistic and actionable answers.

Distributions are then built around the data and put into the decision support model to conduct simulation. This model will capture companies' designated recruiting process and timeline, and ensure it fits within the boundaries of a given tool set.

Clinical Trial Model ***Milestone Summary Table***

Designed to give the user an easy to read single table for examining system performance across Scenarios

Scenario	Description	FSFV	Elapsed Time (Weeks)	FSFD	Elapsed Time (Weeks)	LSFD	Interim Assessment 1	Interim Assessment 2	Endpoint Event
1	0% Non-producing Sites	1/25/2007	2.41	2/11/2007	49.63	1/24/2008	11/1/2007	12/31/2007	3/24/2008
2	10% Non-producing Sites	1/22/2007	2.44	2/8/2007	54.82	2/27/2008	11/10/2007	1/13/2008	4/16/2008
3	20% Non-producing Sites	1/29/2007	2.46	2/15/2007	59.21	4/4/2008	11/18/2007	1/26/2008	5/12/2008
4	30% Non-producing Sites	1/26/2007	2.31	2/11/2007	66.66	5/23/2008	11/30/2007	2/16/2008	6/14/2008

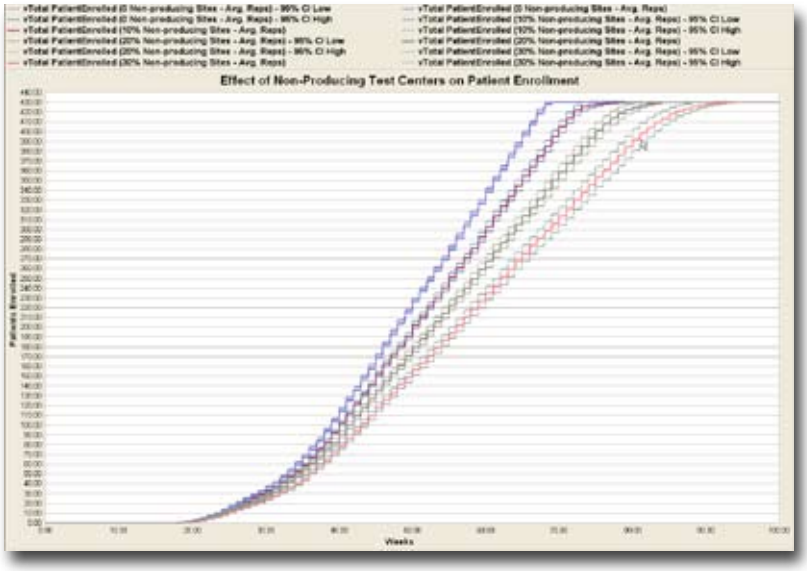
This set of scenarios shows the impact of varying percentages of non-producing sites on the study milestones.

PUSH AND PULL

Once the protocol is prepared and approved, and data fully entered, testing begins in one of two ways. The 'push' method involves putting the information in the simulation technology tool, and running multiple scenarios to determine project deadlines. This produces site enrollment and patient recruitment curves with future confidence intervals. The 'pull' method, on the other hand, tells managers the best set of inputs for reaching a given goal, and achieving cost savings. This step helps determine the optimum test center combination for a given protocol, often at the lowest possible cost or the earliest required date, since these two measurements are often mutually exclusive. It also takes into account the delay time from site

selection until the start of patient enrollment due to regulatory requirements for each site.

The information is typically relayed on a scaled-up recruitment prediction curve that pinpoints the cycle's milestones and goals. This includes first subject first visit, first dosage final subject, final dosage, and the endpoint event, or the point when the final patient exits the study population.

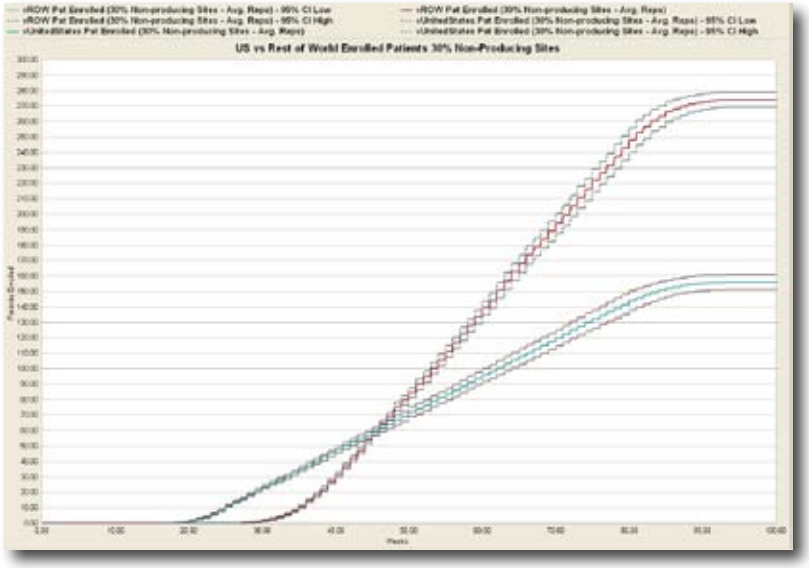


This chart example shows the effect of non-producing sites on patient Enrollment; studies range from 0 to 30% non-producing sites; patient enrollment curves displayed with 95% confidence interval.

Decision support technology like Clinical Trial Simulator can also be expanded to include the patient screening protocol for most therapeutic areas. This option is helpful in cases where data is available on the different criteria that can result in patients being disqualified from participating in the clinical trial. This data can be combined with the projected patient screening volume to projected patient enrollment in the trial. The technology then tracks this population of randomized subjects until they complete the designated requirements for treatment and monitoring.

CONTINUED SUPPORT

It's important to note that while simulation technology is used most effectively from the beginning of a clinical trial, it can be implemented at any stage of the trial. Once the enrolling sites have been characterized for patient enrollment rates, simulation can also be used to create a patient enrollment curve along with a projected completion date. This curve can be used to continue to track the progress of the trial and function as both an early warning indicator and a corrective action method.



Comparison of US vs. Rest of World patients enrolled with 30% non-producing test centers with a 95% confidence interval.

CONCLUSION

Even at its best, the site and patient recruitment process is highly variable and risk-ridden. Clinical trial simulation helps pharmaceutical companies find the right answer the first time around, and much more quickly than with traditional methods.

When implemented effectively, clinical trial recruitment initiatives such as Clinical Trials Sim-

ulator significantly reduce timelines and meet recruitment targets ahead of schedule. And that means the product is one step closer to hitting the marketplace and achieving rapid ROI—the ideal outcome.

CONTACT PROMODEL

Clinical Trials Simulator is the only tool that offers the combined benefits of scenario planning and simulation in one single solution, allowing you the predictive analysis necessary to accurately and quickly quantify the impact of your decisions in the phases on clinical trials, before implementation actually begins! ProModel's Clinical Trials Simulator helps pharmaceutical companies make better decisions, faster!

For more information on simulation use in clinical trials and how CTS can improve your clinical studies, please contact ProModel at 1-888-437-0925 or pharmaVAO@promodel.com.

Visit ProModel online at www.promodel.com.