The Pulse on Global Trials By Matthew Howes

Does geographic expansion increase or reduce the risk of clinical trial failure?

Data recently published by Citeline suggests a correlation between trial success and expanding geography, particularly in emerging markets. As the number of trials continues to grow outside of the U.S. and Europe, this seems to be a promising strategy for improving trial success. But will adding new countries give you the confidence to say you've reduced your risk?

Look at the numbers and you'll see geographic expansion is only one piece of the pie. An analysis of 5,000 terminated trials showed 30% of phase III study terminations are due to enrollment difficulties, making patient recruitment the leading cause of trial failure.

Given that nearly 80% of clinical trials fail to meet enrollment timelines, according to Cutting Edge Information, it is clear the challenge has less to do with patient availability in a given region than with our ability to accurately forecast what will be required to enroll them.

Companies begin trials with a false sense of what to expect. Trial enrollment forecasts are faulty and rarely are completed according to plan. Site feasibility often is inefficient, contributing to inaccurate estimates.

The problem is that the current approach relies heavily on an outmoded paper survey of investigators. Those who respond provide unverified, rough estimates and may be overly optimistic about their ability to enroll patients. Those who do not respond may have the more productive sites, but you'll never know. In the end, 37% of sites under enroll, and 11% fail to enroll any patients at all, according to a 2013 Tufts CSDD Impact Report. We can do better than that.

Meeting expectations

There is roughly a 50/50 chance a trial will meet enrollment expectations:

- 11% fail to enroll a single patient
- 37% under enroll
- 39% meet enrollment expectations
- 13% exceed enrollment expectations

Source: Tufts CSDD, Impact Report, 2013 <http://csdd.tufts.edu>

For decades, industries such as energy, construction and aerospace—industries that undertake major projects of the same scale as global clinical trials—have relied on statistical analysis to forecast completion times with scientific accuracy. Drug developers should follow their lead.

Instead of taking self-reported investigator guesstimates at face value, sponsors should conduct rigorous feasibility assessments using real data to determine the probability of enrollment outcomes. Instead of waiting for sites to miss enrollment targets, consider interventions, such as patient recruitment marketing campaigns to improve on your baseline forecast. Instead of managing unrealistic timelines, revise your probability estimates so target dates and numbers are attainable outcomes, not hopeful ambitions.

A variety of global data sources are available for more accurate estimates regarding the availability of patients. Here are a few:

- PhESi, a global investigator performance database of over 400,000 investigators, extracts data from over 50,000 sources including investigator CVs, regulatory submissions, company web sites, publications and longitudinal views of clinical trial registries. The tool's scoring algorithm has been tested in over 100 clinical trials across multiple therapeutic areas. In all cases, there was a positive correlation between the score assigned and the number of patients enrolled per site. In addition, high-performing sites tend to produce better quality, as measured by data queries resulting in data changes.
- ViS is a global investigator database with interactive visualizations to enable trial planners to navigate analytics about site locations. It can be leveraged to streamline the investigator on-boarding process and create visibility into the progress of active feasibility projects.
- Citeline has the largest collation of public domain global clinical trial and site information available. It assists in providing granular detail to compare and contrast like studies to better assess potential country mix and competitive landscape, and can help identify sites that can be approached for feasibility based on their experience in a given indication.

Before undertaking your next global clinical trial, ask yourself and your colleagues: Are we sure our forecasts are right? Have we statistically validated our risk? Are we planning for success, or have we set ourselves up for failure?

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