SCRIP 100

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RISKY BUSINESS: TARGETED MONITORING OF CLINICAL SITES

in partnership with PAREXEL®

Risk-based monitoring of clinical sites has been gathering in momentum in the past few years. Following FDA guidance on the subject, software providers are now developing systems more sophisticated and intuitive by the day. **Jo Shorthouse, Scrip 100 Editor,** talks to PAREXEL Informatics about its approach to the subject.

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When the FDA released its draft guidance "Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" in August 2011, it opened the floodgates for other regulatory bodies to formally recognize the potential of targeted monitoring at clinical sites, as well as study sponsors.

This guidance had been preceded by sponsors and clinical research organizations (CROs) striving to find more efficient ways to monitor clinical sites than just regular visits by the CRA. In these straitened times, all established processes within the clinical research industry are under scrutiny and site monitoring is no different.

Risk-based monitoring, targeted monitoring, or remote/centralized monitoring – three ways to essentially achieve the same thing: more efficent utilization of on-site monitoring resources and the leveraging of remote monitoring of sites. Research sponsors invest heavily in monitoring clinical trials, ensuring that each patient, each study and each site is reviewed systematically. However, it is fast becoming obvious to those in the industry that just because a site review is thorough and regular, this doesn't necessarily correspond to data quality and patient safety.

The strategy of reducing on-site monitoring visits and upping in-house monitoring approaches has been used to bring efficiency without reducing the quality of data reported or patient safety. But how do research sponsors decide which sites would work well with this strategy, and which are just not suitable? All trials are not created equal, some are naturally more risky than others, and some patients need more intense monitoring than others. As with all things in clinical research, it is the data that hold the key.

TWO IMPORTANT ELEMENTS: ONE SINGLE SOLUTION

Data gathered through eClinical software such as electronic data capture (EDC), randomization and trial supply management systems (RTSM) and clinical trial management systems (CTMS) can create a patchy picture of the site risks for the sponsor to base its decision on. It becomes clear, then, that a holistic and fluid system is needed to ensure safety is upheld, while efficiencies are made.

It is exactly this ethos, of flexibility and embracing the available data universe, that has been driving the PAREXEL Informatics product development for its new My Trials Targeted Monitoring software. It is a system that "will provide a single, unified solution for the management of risk-based monitoring across studies that hasn't yet been seen on the market," explains Liz Love, product director for the development.

The software is being developed to identify risks within a study, that will have an impact on the running of a clinical trial and may even have an effect on the outcome of the trial overall, and then have planned mitigations for those risks built into the system. The risks identified by the system will be based on several pieces of data, both operational and clinical. For example, perhaps a site may not be filling in the expected amount of data on time, or a serious adverse event could be recorded.

Once the risk factor has been plotted into the equation, the second element not to be underestimated is the CRA workload. A key differentiator in the software currently under

development by PAREXEL is the ability to do just that. A unit of time is assigned to each CRA task to calculate the workload needed, the number of tasks needed is then multiplied by the time it takes to do them and the workload score is generated. The algorithm working within the software uses this figure, plus the risk score, to produce an overall indication of a site's general 'health'.

The human element to decision making should not be underestimated. Using a cross-study approach, and therefore having a better understanding of CRA workload, and geographical factors, means that monitoring decisions are not made in a vacuum, but in a real-world scenario.

SITE AS STUDENT

"Once an issue at a site is identified, you are required to do something about it," says Drew Garty, senior director of innovation and strategic accounts at PAREXEL. "The procedures to correct and document issues are both highly regimented and very costly. We can increase quality by measuring more and more frequently, once you are able to detect and understand the propensity toward an issue occuring, you can leverage standard risk processes in place of issue resolution. In other words, manage the risks earlier to avoid the issues."

Mr Garty uses the analogy of site as student. "You can measure a student's performance through a simple test, but this test doesn't tell you if they are improving or decreasing their knowledge. For this to be found out, we have to compare tests over a number of weeks and we can start identifying a trend. Then we can start to compare that student to other students in their peer group," he says.

In Mr Garty's example, he talks about contacting the sites that have been underperforming based on risk measurements to see if there is some support that can be offered remotely or through CRAs. However, it is vital to understand the whole picture, and measure a site's performance based on many different risk factors. "You have to look at all the student's test scores across all courses taken and see if they're on track, or if you need to worry about them. And the same applies with our sites; we record all of the scores, keep all the historical data and are then able to analyze across all of it. We are able to compare the sites to each other and make a decision about intervening in a much more holistic way," he explains.

The student analogy is an interesting choice. Many students throughout the globe now receive their education online. Students in remote countries and regions, just like clinical sites, are now taking online courses, and so if you take all that data you might see that there are certain regions that are having more difficulty than others. It could be a language barrier; it could be teacher turnover rates at the school are an indication of something problematic. "Because we manage our sites globally, we can see trends not just with a single site, but across sites, monitoring teams, and clinical studies," Mr Garty explains. "We can look at the data in lots of different ways with data visualization tools, these can identify signals that will help us manage all of this risk and ultimately improve study quality."

This data visualization is a pivotal part of our new tool. "We can have a lot of information and data on the screen in a way that's very easy to digest, easy to understand and almost makes your decisions for you, or at least makes it very obvious what those decisions should be," explains Ms Love. "It should make it very obvious which are the sites that are outliers based on those trends, which are the sites that really need action taken with them, and the reasons why they need action."

Ms Love explains that a key part of the system is the intuitive nature of the usability. My Trials Targeted Monitoring will not only give its users the data in an easy-to-use format, but it will allow them to drill down into the details and help them to find the best course of action for each piece of data, and the data taken as a whole.

TRANSCELERATING RISK-BASED MONITORING

In June, TransCelerate BioPharma – an independent company formed by the 10 leading pharma companies to make the clinical trial process more efficient – released a position paper on risk-based monitoring methodology. The non-profit organization believes this approach could "significantly modernize and streamline the way studies are conducted and monitored."

TransCelerate's recommendations are driven by centralized and off-site monitoring techniques, as well as adaptive on-site monitoring. The company says it "makes it possible to oversee study parameters holistically and maximize on-site monitoring findings, bringing into balance effort and value gained, while mitigating risks and detecting any issues early, or preventing them entirely."

The methodology used in this position paper has a direct correlation to the system in development by PAREXEL. However, Mr Garty believes that the PAREXEL Informatics system will go a lot further than the plan currently in TransCelerate's paper.

"We know, based on our own experience that every sponsor has its own definition of risk and certain studies do require additional risk indicators," he says. With so much expertise already in-house, it should mean that a system made by the very people who will be using it should specifically cater to all eventualities.

"The focus of your monitoring activity is not static. As an example, if a study participant dies and it is believed to be drug related, the focus on monitoring often shifts from the full range of monitoring activity to focus on patient safety. Because of that, the whole system needs to be fluid and flexible. And so we're taking that into account in the design," Mr Garty explains.

However, there are certain elements that cannot be taken into account in the design, such as the way it is used by clinical research associates (CRAs) or clinical monitoring associates (CMAs). Overall, PAREXEL employs close to 5,000 CRAs and CMAs combined – to ensure that the system can provide the most accurate picture of a research site to the research sponsor it has to be used correctly and thoroughly. Before the rollout of the software in 2014, the CRAs' way of working on a daily basis has to be analyzed and perfected, a herculean task by any standards, but Mr Garty is positive that once the system matches the behaviors and we understand the relationship between risks and issues, there is no stopping the rise of risk-based monitoring.

MY TRIALS TARGETED MONITORING: WHAT WILL IT PROVIDE?

- An overview of study health from a monitoring perspective
- Assistance in the prioritization for on-site monitoring visits and centralized monitoring activities
- Decision tools to plan and schedule monitoring activity
- Oversight of monitoring activity decisions during the course of the study
- Predictive analytics to refine the decision making process
- Strong visualization of data to enable easy decision making