Trials Limber Up

When sponsors are challenged by soaring costs and lengthening timelines, John M Hudak of Criterium, Inc analyses the philosophy and science of 'agile' clinical trials

As President and Founder of Criterium, Inc, John M Hudak has 35 years of progressively responsible research and business development experience in both the corporate pharmaceutical and contract clinical services sectors. He has served as Vice President for New Business Development for Pharmaco (now PPD), Manager of Business Development for G.H. Besselaar (Covance), and Manager of Clinical Development for Riker Laboratories (a division of 3M Pharmaceuticals). John has led workshops on diverse subjects, such as protocol development, information capture and utilisation, and project management for the Institute for International Research and other organisations, and has led seminars in site selection and real-time data management. John has a Master's in Business Administration, a Master's in Biology, and a Bachelor's degree in Zoology.

The incorporation of modern technologies in clinical trials has been shown to yield major cost and time savings to the process of clinical research when understood correctly and applied skillfully. Yet even the most modern technological approach to research will fall short of optimal performance if the people using the technology are not fully prepared and the processes to maximise technology's benefits are inadequate. This article suggests a fresh look at methodology and performance, encouraging an 'agile' approach to clinical trials. Such an approach to conducting trials incorporates the philosophy that:

- Technology is an important component but it is not the single solution required; as more studies become global in scope the technologies used must be reliable for any given region
- Workflow and processes that fit the technology are crucial
- A study team working together – embracing information technology and sharing that information ('breaking down the SILO approach') will yield the greatest benefits when employing modern data collection techniques

When all of these components are working together, the result is real-time management, review and integration of clinical trials data into a single co-ordinated database so that sponsors and their research partners can make timely and relevant decisions about the conduct of clinical study or a series of clinical trials.

CONTRASTING 'AGILE' WITH ADAPTIVE TRIALS

Recently much has been said about the 'adaptive' approach to clinical studies. At first glance 'agile' can sound like 'adaptive' to some, thus it is important to make sure that the distinction is clearly made because the two approaches could not be more dissimilar.

In general, an 'adaptive' trial is one in which data is unblinded, revealed and analysed at one or more points in a given study. There is some thought that this 'sneak preview' approach will enable sponsors to make mid-course corrections to the study design or protocol, perhaps eliminating various non- or mal-performing categories, and as a consequence save time and money that would otherwise be spent 'playing out the string'. This approach is actually under review by entities such as the US Food and Drug Administration (FDA) in an attempt to find balance between the need for time and costs efficiencies for researchers, and health and safety issues for trial participants and ultimately end-users.

This approach is resisted by those statisticians who are concerned that every time you take a preliminary look at data, you in fact change it. Making judgements based on a reduced sample size is contrary to the intentions of a well-thought out protocol that has the advantages of statistical relevance, the luxury of time and a diverse universe of participants for the outcomes of a given compound, device or treatment method to emerge.

While this is a worthy debate, the 'agile' approach focuses on the areas of clinical studies that can be modified and corrected as soon as they are identified. It focuses on the procedural flow, and examines the performance of people, processes, and technology involved in a clinical study, with the overall goal of aggressively monitoring time and cost without shortcuts or compromising any aspect of study design. This approach will particularly focus on studying participant behaviour, geography and other factors that emerge in sites in the field that impact timelines and therefore cost.

'AGILE': HOW IT WORKS IN THE REAL WORLD

In an 'agile' clinical trial, at its simplest level, data is received from various sources and sent to a central location where the data is reviewed, edited, queried and then applied to a working

database with the data which had been received previously (and subjected to the same daily procedure). In the context of this unified database, each daily update is compared to data that already exists in the database. Out of this process, a clinical study team derives two major decision-making tools:

- Each morning you should expect that a snapshot of how your study is progressing, how sites are performing and how patients are behaving
- During the day, you should have the ability to make decisions that affect the study immediately

By cleaning and examining the procedural flow of a study as it arrives, sites can be managed from a distance based on their productivity in terms of patient enrolment, data completion and accuracy of the information they are providing.

DATA COLLECTION TECHNOLOGIES: WHICH IS BEST TO USE?

The 'agile' approach has no 'favourite son' data collection method. They all have good and bad points regarding utility and ease of use. The most important aspect of this is to assure that the combination of forms (IVR/web board, PDF forms, smart fax forms, web forms, and/or VPN reporting) and the data collection and transmission vehicles used (email, fax machines, internet, telephone, and/or Citrix) are the most technologically efficient for the given geographic region that the study is taking place, without overwhelming the area with technological tools that cannot be maintained.

In other words, when looking at the sites where your study will occur, it is vital to maintain a balance between hampering people and processes with technological bottlenecks that result from a lack of capacity negatively impacting your timeline, whilst being aware of and avoiding overcapacity situations, in which highly advanced technological approaches are employed in a region that cannot yet handle it, resulting in increased expense to the sponsor. The 'agile' approach aggressively seeks the most efficient method, or, as is frequently the case, combination of methods to find the best mix for a given study.

As an analogy, let's think of transportation – rather appropriate, after all, much of the clinical research cost is transporting clinical data from the sites to the study database. To get to places we walk short distances, drive cars and motorcycles, ride buses and subways for intermediate distances, and fly for still greater distances. Each time we choose a mode of transportation, we make a value judgement based on cost, time and complexity of process. When we make a trip, we may use all modes of transportation to get to our destination.

Different data collection methods introduce differing amounts of precision and complexity, cost and time. If a data collection technology like EDC or web forms requires a change in process at the site, then it necessitates training of the site because of the increased complexity involved. Training needs to be reinforced, so the workflow of the management company should incorporate multiple and timely training reinforcement sessions as part of the process in order to allow data to flow into the database on time. Frequent feedback to the users and managers of the technology increases the chances of success, but also increases the overhead costs.

EDC forms can also introduce undesirable changes in the workflow for monitoring and data management. Some EDC requires the flow of data to go through the monitor, who must then take on more of a data editing role. Only after the monitor reviews and approves data can the data be managed by the data management department. Since the monitor is a scarcer, more expensive resource, this can actually slow down the real-time aspect to managing and reporting the data.

Traditional paper, fax scanable forms, web-enabled forms and IVRS all require training of various degrees in order to understand how to input the information. All should be examined in the context of the existing skill-set of a site before deciding on the ways to go.

For instance, traditional paper requires training in how to complete the data fields; and the process is lengthened by having to wait for the clinical monitor to visit the site to review the forms. Fax scanable forms require similar training to traditional paper, but you have the opportunity to receive the data centrally in a more timely manner. However, there is a change in the workflow; when the form is completed, the site staff must walk to the fax machine and send it to the central database before it has been reviewed and corrected by someone else. This simple workflow change can produce anxiety unless the feedback from the managing company makes it clear what the workflow will be and how quickly they will hear from the

...when looking at the sites where your study will occur, it is vital to maintain a balance between hampering people and processes with technological bottlenecks that result from a lack of capacity negatively impacting your timeline, whilst being aware of and avoiding overcapacity situations, in which highly advanced technological approaches are employed in a region that cannot yet handle it, resulting in increased expense to the sponsor.

company. Within days, the site finds out that their diligence pays off in rapid resolution of data problems and feedback on how to complete the data from a central location in which the rules for entering data are also reviewed and tracked every day.

EDC methods can produce even more anxiety because there is a complex programme that is put in place; and while there is immediate feedback during the process of data entering, there is pressure to enter data, (a function that has not been traditionally a part of the site's responsibility) as soon as the patient visit is complete. However, in many cases, the sites are either required or choose to complete a worksheet to make the data entry easier. This is an extra step for the site and adds to the monitor's checking burden. For high enrolling sites, this may require additional staff, and longer monitoring visits – costs which sponsors are not always willing to pay.

In global studies, we see that the ability to combine various data collection source materials with a standardised, centralised workflow is the best way to keep the timelines on track and the costs in line. This 'agile' approach embraces all available data collection techniques, choosing the best available to do the job required in the most efficient manner.

The key to making this work is a unifying data analysis scenario that blends different source material, then processes and cleans data in as close to real-time as possible. Ideally, one should have a daily picture of how all the various components of a study (enrolment, patient/site reporting patterns) in order to react in a manner that keeps the trial running on its most efficient schedule.

THE 'AGILE' ADVANTAGE

If we are successful in getting the sites to buy in to the real-time data entry and feedback philosophy, the advantages are numerous:

- You have the ability to affect behaviour – as the data is coming in faster than ever, the processing needs to keep up to that speed. When that happens, the feedback to the sites shows the motivation of attention to detail, and the sites eventually learn to respond to feedback that is coming to them in real-time You can collect real-time data in various ways – Whether using IVR, fax, web or any other, integrating into a centralised database allows the study manager the flexibility to choose what works best at each site.

- Reports are easy to design and review for information – the synthesised data can be made available to clients on a more consistent and timely basis, whether through the internet or a virtual private network (VPN) to allow client access 24/7/365.

- Data can be observed and managed anywhere – as more people plug and play anywhere in the world, you are not as dependant on the site visit, a single monitor or one data processing location for your data flow.

- You can recruit where the patients are more plentiful or seasonal – the developing countries provide an opportunity to boost patient enrolment and in many cases (as with seasonal allergy studies) complete studies faster and earlier because you are not locked into using a system that would be unworkable for many of these areas.

- All your systems can operate as needed 24/7/365 – this includes collecting the data, processing the data, and reporting the information around the clock.

- Development of metrics to increase data quality – with this constant attention to detail, you end up developing ancillary databases that measure monitoring, site and patient behavior. Underperformers are bolstered with help to positively improve performance.

- Decision points can be built into the protocol – the point of most Phase II and Phase III studies is to evaluate efficacy and safety. Once all parties are confident in the flow of data, a well-designed protocol can build in statistical decision-points to provide greater safety or improve patient care either in a blinded fashion to test statistical variance by managing the data daily or by providing the information for unblinded monitoring to a third party data management board. This serves the purpose of many 'adaptive' trial designs without controlling the results of the study, and has the side benefit of insuring the most consistent reporting across patients, sites and studies.

CONCLUSION

Today's clinical research environment is competitive and expensive. There are competitive products in the clinic. There are marketed products that patients have access to, thereby making it more difficult to find valid patients and to entice valid patients into clinical trials, particularly when the study is placebo-controlled.

Once you have a patient in a study, you want to do everything possible to ensure that the patient complies with the protocol for the duration of the study. If a patient is non-compliant, you can correct that patient's behavior before the data becomes unusable and influence the protocol specific compliance of patients who are enrolled after that patient.

An 'agile' approach that yields real-time data is one such way to manage the study daily before non-compliance becomes too costly. Not only can you do this for patients, but you can do this for the sites, clinical labs and monitors – maximising the efficiency, accuracy and frequency of data completion. Instead of having data that is received weeks to months later before we could compare, correlate and correct inaccuracies, we can now set up systems that require data to be received centrally on a daily basis. ◆

The author can be contacted at jmhudak@criteriuminc.com