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NEXT GEN EDC **Tools Supporting Adaptive Trials**

By **Graham Nicholls** and **Bill Byrom**

Every trial has them: planning, execution and analysis. Within those three steps, one wrong move is accompanied by surprisingly steep penalties. An entirely new study or set of studies may need to be designed and executed.

Take one example. Bringing the wrong dosage into Phase III can result in terminating an entire program prematurely. Or, if the drug with the wrong dose does reach the market, there are major implications for patient safety, as well as pricing and reimbursement. The journal *Nature* has estimated that one in five marketed drugs is launched with a flawed dosage.

So the opportunity to adjust a clinical development program in mid-study is a major advance. Hence the growing interest in the adaptive clinical trial. The PhRMA Working Group on the topic has defined an adaptive trial as “a multistage study that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial.” Regulatory bodies have endorsed the technique, with the usual warnings and caveats.

A New Way

The early notions of adaptive designs included two-stage trials, group sequential designs and blinded sample size re-estimations. Now the concept has expanded to embrace dropping or adding treatment arms or doses; changes to the treatment allocation ratio; changes to the interim analysis schedules; changes in objectives (e.g., switching from non-inferiority to superiority; and changes in primary endpoints.

Of all of these, modifying treatment arms and ratios is, in our view, one of the more exciting and revolutionary techniques. By designing studies with these options built-in, it is possible to both enhance the selection of optimal dose in Phase IIIb and combine Phase II and III into a single seamless process, with all of the associated time and cost savings that result from not starting another trial.

Real-Time Data

The ability to provide such levels of flexibility, all based on access to data from different sources, all but requires real-time data and high levels of systems integration, if not a centralized data warehouse or repository.

In the early days of adaptive trials, paper-based case report forms (CRFs) were often transmitted by fax and read by optical character recognition (OCR) technology. There were many practical issues associated with getting data from monitoring visits to a central management area. Checking and cleaning the data before analysis was another hurdle.

New Tools

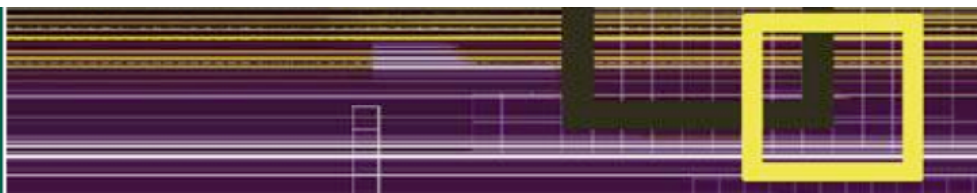
Today, electronic data capture (EDC) systems allow faster assessments of clinical data. EDC has played a central role in adaptive trials for obvious reasons, such as the provision of data checks against pre-defined rules and data clarification capability at the time of entry. In addition, data cleaning is possible throughout the study with all information stored in one place from the outset.

But EDC is not the only critical enabler of adaptive designs. With some studies, the key response endpoint is reported by patients, historically from paper diaries. Major concerns with paper diaries included data quality and speed of access.

Electronic solutions for patient reported outcomes (ePRO) are obvious companion technologies for EDC in adaptive trials. Whether using the telephone-based interactive voice response system (IVRS) or a handheld diary, ePRO can incorporate data quality checks, as well as provide real-time access to data outside clinic visits.

Rapid Randomization

Where EDC or an ePRO solution is not used, speed of access to response data can be achieved more simply. How? Just by collecting this data with the IVRS used for randomization. It is hard to see how an adaptive trial could be conducted easily without utilizing IVRS. Imagine a study in which through time the treatment allocation ratio might change or treatments arms are dropped.



There are unexpected wrinkles, however, that become apparent after the technology is chosen. While supply planning can be a challenge for conventional study designs, it becomes particularly challenging in an adaptive environment.

Drug Supply

Every time there is a design adaptation, we have to ask difficult questions. Are the right drugs in place? Does every site have enough stock to accommodate existing and newly randomized patients? If not, then urgent action will be needed to prevent shortage of drug at the site.

Longer term implications also have to be addressed. With current and potential changes to the randomization scheme, will there be enough of the drug to complete the study? Will there be sufficient drugs at supply depots in each country? Do we need to begin a new packaging campaign? How should that campaign be changed? These questions are more difficult to answer in adaptive trials where future treatment allocations are variable. More and more, sponsors are turning to simulation to provide the answers and make accurate drug supply projections.

It is easy to see why IVR technology has quickly become established as a key element underpinning the successful implementation of adaptive trials. It is ideally suited to support changes in supply strategies, with real-time automated stock control, EDC/ePRO integration and complex randomization methods built-in.

Packaging and Depot Issues

An IVR approach, employing uniquely numbered dispensing units, allows for site and depot stock strategies to be modified easily, reflecting the current randomization algorithm. Traditional supply methods generally require the delivery of large quantities of drugs to the site. But for an adaptive trial, such a bulk delivery could signal the investigator that a design change has occurred. Using the IVR system, low stock levels can be maintained at site and can be replenished as needed. That will effectively hide any design adaptations with respect to drug supply,

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and preserve the blind.

In short, the deployment of adaptive trials is likely to require rapid access to clean data from multiple electronic sources. Collection of subject response and safety data may feature a mix of EDC, ePRO and randomization, all of which are now mature technologies. Yes, paper-based methods have been used in adaptive designs in

the past. But it is clear that the nuances and scale of industry-sponsored research will benefit from the considered use of technology in the exciting era of adaptive designs that is about to dawn.

Graham Nicholls is product manager at ClinPhone, with his focus being the development of randomization and trial supply management technology solutions. He is an industry-trained statistician with over 15 years of experience in the pharmaceutical industry. **Bill Byrom** is VP of product strategy and marketing at ClinPhone, where he holds responsibility for providing strategic direction to ClinPhone's suite of products, including developing new areas of technology applications within clinical trials and health care.