Tipping Point

Dr Michael Murphy at Worldwide Clinical Trials tackles the big questions on the minds of drug development and clinical research professionals, and explores the impact of technology on today's studies

***ICT*: We've heard you say that data acquired throughout the clinical research process must be complementary to clinical care goals. However, CROs are sometimes perceived as caring more about the technology being used to acquire the data than the actual data. Why is that?**

Dr Michael Murphy: Given the business models of CROs, it is a common misperception that the incorporation of new technology into trial operations occurs simply in service to novelty, or in an effort to achieve service differentiation. However, novel data acquisition processes are predicated on an ability to enable the clinical research procedure and maximise the efficiency and value-added activity of CRO staff. There is a strong regulatory endorsement for the use of a variety of platforms in data acquisition, as it provides consistency and reliability and permits innovative approaches to trial design and analyses; additionally, these advances are foundational for participating in various permutations of risk-based monitoring.

New technology that is incorporated within a thoughtful and programmed approach by a CRO facilitates the drug development process (such as study start-up activities or electronic source documents); enables innovative trial designs (like adaptive studies); changes the point of data collection for many types of trials (for example, from clinics to the home); and – most importantly – increases the time available for professional contributions from CRO staff.

The pharmaceutical industry has been slow to take up electronic solutions, despite their revolutionary potential. Many believe the sector is nearing a tipping point – do you agree?

It is said that the art of interventional clinical research is the ability to responsibly evaluate small molecules, biologics and devices inherently unpredictable in terms of safety and efficacy, in the hopes of transforming therapy. Appropriately, the clinical trial process is one that attempts to mitigate risk – a sentiment that extends into the use of technology, making the cautious uptake of various electronic solutions a prudent business and clinical decision. Nevertheless, incremental changes in regulatory guidance and technology have converged with the need for efficient and informative study designs, creating an imperative to re-examine the procedure.

Dr Michael Murphy's (MD, PhD) professional career has spanned 25 years, and his positions within the pharma industry emphasise the integration of medical and scientific acumen with operational excellence. He is board-certified in Psychiatry, and has a Doctorate in Pharmacology. Michael's supervisory responsibilities as Chief Medical and Scientific Officer at Worldwide Clinical Trials are international in scope and include strategic programme and protocol design contributions for translational research activities, particularly for orphan disease indications.

Various regulatory agencies have introduced draft guidelines to remove uncertainty, and shape the direction of technology and the methods for application in the clinical trial process. These include the methods of oversight through risk-based monitoring, the use of electronic source data, and the ability to provide regulatory submissions using standardised study data. Where data acquisition platforms are not patient-facing, rules of engagement seem codified and less controversial, and adoption has been swift. For example, a cloud-based system for data warehousing is readily suited to business documents. In contrast, similar solutions for patient-facing assessments are approached more cautiously and predicated on first addressing reliability, necessity and utility for generating evidentiary standards for safety and efficacy. An ability to use technology intelligently in either observational or interventional research represents a challenge that the industry now fully embraces.

Which technologies do you think will have the biggest impact on clinical research and commercialisation activities over the next 10 years? What do you predict to be the next big development?

In 1949, it was predicted that computers might have, in the not-too-distant future, fewer than 1,000 vacuum tubes and weigh only 1.5 tonnes (1). Forecasting the evolution of technology – and more importantly, how that technology might be applied within the study process – is best entertained cautiously. What can be said, however, is that innovations in how new technology is used – as much as the technology itself – constitute the largest single factor in a technology's eventual incorporation into the clinical trial procedure.

For example, most longitudinal studies have data acquisition procedures demarcated temporally by visit structures. Customarily, these visits occur in a clinic setting, spaced at intervals – balancing the need to address hypotheses with the inconvenience and cost of obtaining the information. What if you could gather data intermittently, or on a continuous basis in the patient's home and across different types of activity – particularly for physiologically-based assessments (glucose or cardiac monitors connected to smartphones, for instance)? In essence, adopt processes in clinical trial design which acknowledge that the beauty in music (clinical research) is as much contained in the pauses between the notes (the visit structure) as in the individual notes (the site visits).

And if that technology was in place, what are the methods that could be employed of assuring meaningful patient compliance, controlling for environmental confounders, to assure the data could be analysed in a fashion that would be informative? Technology and the management of technology that enables this harmony will create beautiful music – and deliver a huge impact on the industry.

In so many ways, the next 'big development' is not in reference to the tool; it is in reference to the methods of using the tool to provide an opportunity for change and differentiation.

How important is it to be able to share data acquired during a trial among patient participants and other collaborators, and what impact can this have on study outcomes?

Within the clinical trial setting, much attention is focused on the technological aspects of data acquisition and assurances of regulatory compliance. Historically, the flow of information is one-way: from the patient to the clinician; to the database for analyses; and, apart from rare exceptions, the process is fully blinded to treatment group assignment. Utilisation of technology to inform trial design prior to study inception, or to communicate information to patients following study completion, suggests possibilities that have not been fully exploited.

Prior to protocol initiation, for example, social media might be used to solicit ideas regarding protocol design before it is finalised, in order to enhance patient accrual and retention. Understanding the realities of patient management and the experience of the illness from the perspective of family and patients assists in the resolution of conflicting data needs in the study design process. In contrast, during study conduct, technology promoting online conversation could jeopardise the integrity of the study. Anecdotes from subjects may imply adverse events, lack of efficacy or inconvenience, negatively impacting trial participation. These unstructured conversations, which can prove invaluable in the design phase of a project, may also inappropriately and inaccurately influence how symptoms are reported during the trial, distorting the implications derived from the resulting database.

Following product registration, quantitative study designs for quality improvement research could benefit from technology permitting distribution of information in a widespread fashion to patients receiving therapy in an adaptive process uniquely suited to that type of research. For example, stepped wedge designs sequentially roll out interventions to clinicians, doctors or organisations to monitor the impact of innovative therapy adoption, while time series designs are useful in evaluating whether a quality

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improvement initiative has an effect in comparison to the secular trend relevant to this particular indication. In these settings, reciprocal exchanges of information between patients, sponsors and providers might facilitate the use of adaptive strategies determining the content and format of information most likely to influence patient and doctor behaviour.

The utility of sharing data, as well as information derived from those data, with study participants varies by phase of development (before, during and after product evaluation), and the methods by which that information is structured.

You’re saying that data acquisition through the use of novel technology can facilitate patient-centric and site-oriented research. How do we make that happen?

Clinical research data are derived from doctor/patient interactions, in which the process of those interactions – including the collected information – are determined by the design of the protocol. Technology that is transparent to those interactions, while also satisfying reliability, sensitivity, various aspects of validity and attribution, can be transformative. However, the skills required to participate in that process, particularly by site-facing CRO staff, are clinical. They arise from an appreciation of patient management issues and site dynamics occurring in clinical research against a backdrop of clinical care. This is particularly important for therapy with breakthrough characteristics targeting unique patient phenotypes, which are commonly encountered in the current research setting. CROs that highlight the importance of clinical acumen through credentialing and training programmes provide a differentiated business model – one which emphasises that technology exists in service to clinical research.


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What is the role of the clinical research assistant (CRA) in that regard? Do you have any recommendations to help them succeed in their roles?

CRAs are specialists in applied clinical research. Emerging technology increasingly permits the CRA and other operational staff to ‘live in the data stream’, while simultaneously enabling monitors to spend more time reviewing critical study-related issues, assessing protocol compliance, monitoring for patient safety, and gaining more insights regarding the impact of novel interventions on patient care. With the introduction of facilitative technology, the ultimate expression of the art thus becomes site management, analytics and monitoring data for medical meaningfulness, as well as integrity. A therapeutically focused, tech-savvy CRO will assist its CRAs in developing these skills by using technology that enhances the benefits that accrue, by allowing staff to remain therapeutically focused.

Therapeutic focus – coupled with enabling technology – helps each CRA gain a deeper understanding of the disease management process, the rationale for therapeutic interventions, and a diverse mosaic of assessments specific to each therapeutic indication that demands informed monitoring. With this perspective, cost savings that come from enhanced technology become a secondary consideration, and value-added monitoring services with a strong clinical orientation by a CRA will be the real differentiator for the CRO.

Reference

1. **Popular Mechanics, 1949**