



The Renaissance in IVR/IWR Systems

Use of interactive response technologies is on the rise

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THE PAST FEW YEARS HAVE SEEN a surge in the use of interactive voice and web response systems (IVRS/IWRS) in clinical trials. Whereas five years ago, technology providers offering such services feared that electronic data capture (EDC) or other technologies may replace the use of IVRS/IWRS, today such firms are seeing rapid growth in the use of their technology solutions. Long gone is the speculation that IVRS/IWRS will fade away.

A number of factors have led to the renaissance in interactive response technologies. Among the most prominent are the increasingly complex nature of global clinical trials, advancements in study designs and methodologies, and matters relating to the cost of conducting biopharmaceutical R&D. We shall examine the growth of interactive response technologies in the context of these trends in biopharmaceutical R&D.

IVRS/IWRS in Context: Translational Medicine and R&D Productivity

Since the advent of the new millennium, the pharmaceutical industry has come under extreme scrutiny by the investment community, trade press, and the general public regarding drug pricing, R&D productivity, patent expirations, drug safety, and slowing revenue growth rates. Some analysts have stated that the pharmaceutical business model is dated and needs to be dramatically changed in order to save the industry from further decline. Others claim the blockbuster business model is dead and needs to be replaced.

Such calls of doom and gloom have muffled the news of positive changes that are occurring in the industry, particularly the new and innovative ways that biopharmaceutical companies are conducting R&D. Under the umbrella of translational medicine, sponsors are employing a range of new tools including adaptive clinical trials, the "learn and confirm" R&D methodology, biomarkers, diagnostics, electronic clinical technologies, and global trial designs. Such innovations in R&D are making an impact on productivity in clinical trials and contributing to the resurgence of IVRS/IWRS.

While there are certainly differences among the various facets of translational medicine, there is one commonality: All rely on the availability of electronic data to improve R&D productivity. Historically, R&D was conducted using paper to collect data during clinical trials, making it very difficult for scientists to share knowledge during individual trials and between various project teams cutting across the major phases of drug development (discovery/ research, preclinical, and clinical development). Today, however, those information silos are being closed in great part due to the adoption of electronic technologies in clinical trials, particularly data stored in IVR/IWR, EDC and Clinical Trial Management Systems (CTMS).

"Learn and Confirm" Methods

One of the most troubling issues faced by biopharma companies has been the high failure rate in Phase III clinical trials. Late stage trials are very costly and consume significant human resources, but are essential to the commercial viability of companies. To improve success rates some sponsors are employing the "learn and confirm" method of drug development. Wyeth has been at the forefront of this new paradigm. During the "learn" stage, sponsors seek to generate as much safety and efficacy information as possible using sophisticated testing involving biomarkers, various diagnostic tools, central

laboratory assays, and other means. Once “proof of concept” is established, Phase III trials are being strategically conducted to “confirm” the safety and efficacy of drug candidates in larger, global studies.

Clinical technologies are playing a central role in the “learn and confirm” paradigm, as data collected electronically can be easily shared across teams from discovery through Phase III. Access to the data allows clinicians to modify course when necessary, improve resource utilization, and make faster, more informed decisions than when using paper for data collection.

Adaptive Trials

IVR/ IWR systems have proven vital to the success of translational medicine efforts, particularly adaptive trials. The IVR/IWR is essential for implementing sophisticated adaptive and dynamic randomization schemes employed in adaptive trial designs. By automating the randomization process, IVR/IWR technologies reduce errors and simplify the process of assigning treatments and managing drug supplies during a clinical trial. Additionally, in order to make mid-trial changes during an adaptive design, clinicians need access to real-time data on patient recruitment, visit schedules, treatment histories, and drug supply information, all of which is collected and stored in IVR/IWR systems. Given their transactional nature, IVR/IWR technologies are able to respond to mid-study inputs by clinicians and subsequently trigger changes in dosages and treatment arms in a seamless manner.

Global Trials

Beyond their importance to adaptive trials, IVR/IWR systems have been vital to the success of global trials. As trials have increasingly become international to improve patient recruitment rates and test drugs in nations in which they will be marketed, IVR/IWR systems have proven to be essential for recruiting, screening, enrolling and randomizing patients, as well as managing drug supply on a global basis. At any given time in a study, sponsors and sites have immediate access to drug supply and patient enrollment and treatment information through the IVR/IWR, allowing clinical trial practitioners to proactively solve issues that formerly presented obstacles to success, such as poor enrollment, shortages or overages of clinical/drug supplies at sites/depots, data on investigator and site performance, and factors involving patient safety. Access to this data, easily integrated with electronic data from EDC and CTMS systems and other e-tools, has facilitated interim reviews of global clinical trial data and lessened the burden of querying prior to database lock.

Biomarkers

Biomarkers are increasingly playing a central role in clinical trials by providing key information that identifies populations or subpopulations in which particular investigational drugs are responsive and effective. Once such populations are identified, treatment arms in adaptive trials can be modified and future trials can recruit patients using more precise inclusion and exclusion criteria. Thus stratification of patients based on biomarker data becomes a viable strategy for successful trials. As the adoption of biomarker-based research proliferates, the use of IVR/IWR systems will likely increase in stride, as both patient recruitment and randomization can be confidently conducted using such tools.

Patient-Reported Outcomes

IVRS/IWRS has also been vital to the success of collecting patient reported-outcomes (PROs). As opposed to traditional research methodologies in which data is collected mainly by study personnel (e.g., physicians, site professionals), modern approaches are increasingly incorporating PRO data to support regulatory submissions, product promotions, formulary submission dossiers, and label claims, among other initiatives. IVR/IWR systems are used along with handheld devices to capture this information and store it in databases for analysis prior to regulatory or formulary submission. IVR/IWR is a highly flexible technology because it uses both traditional methods (telephone) and contemporary approaches (Internet/Web) to capture data, thereby allowing trial sponsors to generate information in territories that have particular technological barriers. Moreover, having the flexibility of choosing among data capture options is particularly important when working with diverse racial, ethnic, and elderly populations that have differences in technology or language skills.

Financial Aspects

Impacting IVR/IWR Utilization

It is estimated that it costs approximately \$1.2 billion to develop and bring a drug to market (including the costs of failing drugs). Given that reality and the declining rate of drug approvals during the past 10 years, biopharmaceutical companies are seeking ways to reduce development costs and are increasingly turning to technology as part of that effort. IVR/IWR in particular is being increasingly applied to help offset costs and improve trial productivity because it offers cost-effective solutions to better manage two key elements of a clinical trial: Patient enrollment/screening/randomization and supply chain management.

Developing Expensive Biologics

One of the factors driving up costs of development is the increasing number of biologics in the pipeline. Biologics are far more costly to develop, test, and manufacture than chemical entities for a variety of reasons beyond the scope of this article. The use of IVR/IWR to manage biologics during clinical trials is one method that sponsors employ to control costs.

Once a biologic is developed and enters testing, cold chain storage is one of the main factors increasing the cost of preclinical and clinical studies. The logistics of cold chain management are made far easier through the use of IVR/IWR systems that contain inventory management functions and can track the drug across its life cycle from initial manufacturing to eventual patient usage, return, and destruction. Closely monitoring and managing re-evaluation or expiration dates with IVR/IWR technology is particularly helpful in reducing the cost of testing biologics. Other creative efforts, specifically drug/product pooling, may also be employed.

Drug Pooling

Drug pooling is a relatively simple concept, but it can be difficult to implement. Basically, pooling of investigational drugs involves the use of a common inventory that is shared across multiple studies. The supplies are held at the depot (typically unlabelled) or site level (labeled) or a combination of the two within and across studies. Traditionally, supplies are allocated and managed for individual studies, which does not allow for easy transfer across studies because of the assignment of kit numbers and labeling of individual kits on a depot level. When study materials are kept in a pooled environment, "just in time labeling" is possible, allowing for the same inventory to be used across multiple studies.

The benefits of drug pooling involve both cost savings and increased efficiency in drug supply management during a clinical trial. The most obvious form of savings is the reduction in drug manufacturing expenses – fewer production runs equals less costs. Pooling of supplies during a trial reduces wastage in the supply chain by allowing multiple studies to tap the same source of investigational drug supply before expiration dates render the drug useless. Tapping a single source of inventory also results in less need for safety stock, as it is no longer necessary to keep additional stock for each trial. Moreover, drug pooling can reduce costly delays in trials by preventing shortages of supplies for individual studies and sites, as drugs can be shared and distributed as needed.

Drug pooling also reduces the amount of drug ordering and administrative activities involved in drug management. For cost conscious sponsors, especially biotech firms using cold chain storage for biologics, drug pooling is especially advantageous because it reduces distribution costs and allows sponsors to manage all supplies in one location with one vendor. This convenience translates into reduced drug

wastage because it lessens the chance that study materials will be improperly handled by one of several vendors shipping to various sites across individual studies. Finally, drug pooling reduces costs relating to drug returns at the end of a study. When drug is pooled, there are often fewer products to return, and they are often returned from one location, thereby reducing shipping, handling, and administrative costs.

Drug pooling is nearly impossible to conduct without employing an IVR/IWR system with strong drug management capabilities. Manual management of such complex activities increases the probability of human error, which is vastly reduced by IVR/IWR systems which automatically assign kit numbers, conduct inventory management functions, and hold information relating to randomization, blinding, patient visits, and other key trial activities. Most advanced IVR/IWR systems have drug-pooling capabilities that automate many of these tasks and can be customized for specialized functions.

Patient and Supply Chain Management In Global Mega-Trials

A key trend that has emerged in the age of translational medicine involves conducting global clinical mega-trials to confirm safety and efficacy. By strategically applying biomarkers and adaptive trial designs, as well as intensive central laboratory and bioimaging testing in early stages (see “learn and confirm” methodology above), sponsors feel far more confident in staging large global trials to confirm what was learned about the molecule in proof-of-concept studies. Given difficulties in recruiting the number of patients necessary for mega-trials, sponsors are increasingly designing studies that tap hundreds of sites worldwide, gaining access to fewer patients per site than they have historically, but more patients overall. This strategy is being used by both large and small biopharmaceutical companies that have international R&D operations, or can access clinical trial sites through global CROs.

The complexities of managing patient enrollment, randomization, and drug/clinical supplies management in global mega studies can be intimidating without the use of IVR/IWR. Paper, internal drug management systems, and other sponsor-based tools often prove insufficient to effectively manage these tasks. IVR/IWR by contrast provides a cost-efficient solution that allows near real-time access to data at all times during the study. Moreover, given the challenges of global trials in multiple languages and with different regulatory guidelines across countries, the support of a global mega-trial can be vastly more expensive than automating all of these functions through IVR/IWR systems. Once the systems are set up in native languages and within regulatory guidelines, there are often fewer calls to sponsor or CRO support lines and significantly less regulatory risks.

In an age of global drug development and translational medicine involving a variety of complex designs — e.g., adaptive trials, global mega-studies — and supported increasingly by sophisticated testing—e.g., biomarkers, bio-imaging, central lab assays — the need to access data electronically in real-time has become a necessity. IVR/IWR has proven to be a major force driving innovations in biopharmaceutical R&D because it holds two sets of data vital to the success of a clinical trial: Patient and drug supply management information.

The transactional nature of IVRS/IWRS is one the main reasons the technology has seen an increase in adoption. Whereas EDC, CTMS and other clinical technologies can generally be described as static in the sense that they do not often propel changes in a clinical trial, IVRS/IWRS can be viewed as dynamic and transactional because it sets in motion actions from patients, sponsors and sites. For example, as patients are recruited, the IVRS/IWRS assigns kits numbers and sends drug supplies directly to sites. Sites and sponsors monitor their drug inventory via the IVRS/IWRS and react by re-supplying or returning supplies based on a number of factors. IVR/IWR technology is especially transactional in adaptive trials where changes in treatment arms, drug assignments, and dosage levels are administered by IVR/IWR systems in an automated manner.

In sum, IVRS/IWRS has proven central to the dynamic new approaches of conducting R&D in the age of translational medicine. As pharmaceutical companies face increasingly competitive global market challenges, they will continue to utilize IVR/IWR and other electronic clinical technologies to gain competitive advantage and improve drug development productivity.