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Using IVR (Interactive Voice Response) solutions to streamline clinical trials and save time and money whilst increasing resource efficiency

In the September 1999 issue of PMPS, Eddie Montoya from Covance eloquently described some of the benefits the use of Interactive Voice Response (IVR) systems can bring to clinical trials. His article focused on savings which can be made in the area of clinical trial materials, and while the savings can indeed be great, and can often represent the main reason for employing an IVR system, there are many other reasons why use of such a system can be advantageous to the clinical trial process. Some of these reasons are frequently overlooked since it is not as simple (although by no means impossible) to translate them into 'hard cash' as it is to link savings in clinical trial materials to reduced costs.

These reasons are sometimes viewed as 'soft' reasons but they can add significant control to a clinical trial. It is ironic that in other industries such as retail food, supermarket chains would find it odd that the provision of 'up-to-date information about the performance of all stores was not given higher priority.

The cost of 'lateness' in the clinical research process has been estimated at over US\$1 million per day. Therefore, it is critical that pharmaceutical and biotechnology companies closely examine the time and effort they spend carrying out laborious, repetitive and time-consuming manual tasks which could be better performed using modern IT systems.

This article will describe a case study based on a trial for which ClinPhone recently operated an IVR system. It will also attempt to open up the thinking process on the subject of the broader benefits of using IVRS in clinical research. In this project, reduction in clinical supplies wastage was indeed a factor for the use of IVRS, but even without this benefit, the project's successful implementation would have been much more difficult without the use of such technology.



By Jonathan Engler, Co-Founder of the ClinPhone Group

Jonathan Engler is one of the two Co-Founders of ClinPhone Group, the independent provider of electronic trial management systems utilising IVR and web-based technology. ClinPhone was founded in 1993 and now has operations in Nottingham, UK and Princeton, New Jersey. Prior to starting ClinPhone, Jonathan spent three years working in Phase III clinical trials for a heart-failure compound at a UK-based pharmaceutical company, before which he was a hospital-based physician.

OVERVIEW OF THE TRIAL DESIGN

This was a double-blind study comparing placebo and the active drug, administered intravenously to approximately 450 patients with septic shock. The study consisted of several dose cohorts, and was designed so that a safety analysis needed to be performed by an independent group at the end of each cohort before proceeding to the next level. During the time between the closure of one cohort and opening of the next, no patients were to enter.

In order to create the optimal balance between treatment groups - and therefore reduce the numbers of patients required by maximising statistical power - a complex adaptive allocation scheme was used which balanced four key prognostic indicators.

The calculation of dose was relatively complex and depended on the patient's weight as well as the cohort active at the time.

The drug was in very short supply. There were three vial sizes - 4ml, 10ml and 20ml. Only 4ml vials were available from the outset, and the larger vials became available later. Moreover, all drug was due to expire halfway through the trial (!) and would therefore need replacing with new supplies.

The study was being conducted in the UK, USA, Canada, three South American countries and Australia. Each country had an in-house distribution depot responsible for resupplying its sites, with the exception of the South American sites which were supplied directly from the USA depot.

ClinPhone was used in the study of the following

- Initial site activation, shipment request and
- Randomisation and checking of key inclusion
- Calculation of dosage based on patient's weight and optimisation of vial usage
- Automated generation of drug shipment requests to adequately re-stock sites and depots, tracking drug arrival at intended destination
- Provision of reports to enable rapid collection and replacement of expired drug
- Provision of tracking data to management
- Provision of unblind and key outcome data (death rates) to Safety Monitoring Committee
- Closure and re-opening of cohorts
- Final study closure
- Provision of vial-by-vial data enabling simple but full drug accountability following the call."

"The patient's weight was entered at enrolment and used to calculate the proper dosage. Then, based on the principle of using the least amount of drug, the optimal combination of vials from those available on-site was specified. The system then read out ID numbers and volumes to be taken from each vial, with a confirmation being faxed to the site automatically following the call."

Initial Site Activation. Shipment Request and Arrival Tracking

The country monitor dialled into the system to register new site activations. During this call they estimated the site's recruitment rate (fast, medium or slow), as well as the site's local storage capacity (the drug required refrigeration). The system automatically sent (via e-mail and fax) a request to that site's depot requesting the shipment of an appropriate quantity of drug that had been calculated by the system. Upon arrival, a staff member called the system to confirm receipt of supplies. This allowed management reports highlighting unfulfilled orders to be generated on a

Benefits

- Since this process was rapid and well controlled, no pre-loading of sites with drug prior to receipt of necessary approvals was allowed to occur (a GCP/safety/ethical benefit)
- The site's initial supplies were tailored to their likely needs and capacity, resulting in minimal wastage, yet not allowing shortage of drug
- Sponsor personnel could focus their efforts on following up on shipments which had not arrived, rather than wasting time chasing the site for confirmation that drug had arrived, since this data was highlighted in the reports

Randomisation and Checking of Key Inclusion

During the randomisation call, the investigator entered key data about the patient. This information was used so that non-compliant subjects could not be enrolled. An adaptive allocation method was employed to determine the treatment group allocation for each patient.

Benefits

- Entry of non-compliant patients was minimised, saving tens and possibly hundreds of thousands of Dollars. The improved balance created reduced the number of patients required to reach the desired power, resulting in an ethical as well as economic benefit

Calculation of Dosage Based on Patient's Weight, and Optimisation of Vial Usage

The patient's weight was entered at enrolment and used to calculate the proper dosage. Then, based on the principle of using the least amount of drug, the optimal combination of vials from those available on-site was specified. The system then read out ID numbers and volumes to be taken from each vial, with a confirmation being faxed to the site automatically following the call. During the trial, this algorithm was adjusted to account for an anticipated shortage of one of the vial sizes, therefore ensuring all vial sizes were available throughout the study.

Benefits

- Elimination of site errors - very common in these type of studies-in dosage calculation
- Use of optimal combination of vial sizes

Automated Generation of Drug Shipment Requests to Adequately Re-Stock Sites and Depots and Tracking Drug Arrival at Intended Destination

Throughout the trial, the stock levels of all vials were automatically monitored. When certain predefined triggers were met, restock requests were generated. These were then tracked in the same manner as the initial shipments. A similar process operated to ensure adequate resupply of country depots from the

Benefits

- Study sites did not run out of medication or hold large amounts of wasted stock resulting in the optimised use of available raw drug
- Large numbers of shipments could be closely monitored, with rapid early alerts of supply problems
- Tracking of supplies at the depot allowed for early warning of the need to label new supplies in the appropriate languages

Reporting which Enabled Rapid Collection and Replacement of Expired Drug

The system held the position of every numbered vial in the world. Managing the replacement of expired drug was therefore a much simpler task than it would have been without this data. Controls were programmed into the study to prevent the accidental allocation of expired medication.

Benefits

- The likelihood of accidental use of expired vials was minimised

Provision of Tracking Data to Management

Reports at various levels of detail were provided. At a high level, country and study recruitment could be closely monitored. At a more detailed level, recruitment at individual sites could be tracked.

Benefits

- Rapid closure of poorly performing sites and concentration of effort at the most productive ones was made possible
- Using traditional tracking methods, recruitment data is often weeks out of date, hindering the management process
- Managers were able to view real-time data over the Internet, as well as receive daily reports by e-mail

Provision of Unblind and Key Outcome Data (Death Rates) to Safety Monitoring Committee

After each cohort, the SMC received unblind data and data on deaths which had been registered into the system by investigators.

Benefits

- This allowed a rapid and informed decision to be made about whether or not to proceed to the next dose cohort
- This prevented delays between cohorts that would have had an adverse effect on the trial, including deterioration in morale, loss of 'momentum' and using up the limited time prior to drug expiration
- The dynamic balancing scheme employed also ensured treatment groups were balanced for key prognostic factors, even in the smaller subsets making up each cohort

Closure and Re-Opening of Cohorts

When the study was closed for enrolment between cohorts, every investigator was automatically sent a fax to inform them. They were subsequently sent a fax to tell them that enrolment had reopened. In addition, if they tried to use the system to enrol a patient, they were prohibited from doing so.

Benefits

- Accurate control over cohort closure/opening
- Eliminated over-enrolment into any cohort and ensured investigators were informed as soon as new cohorts were opened

Final Study Closure

A very similar process took place at full study closure, preventing any over-enrolment.

Provision of Vial-by-Vial Data Enabling. Simple but Full Drug Accountability

In a process similar to expiration date management, reports were provided which identified the exact location of every vial worldwide. This facilitated the process of final drug accountability.

CONCLUSION

Use of IVR systems can result in large savings in clinical trial material costs. However, the technology can also make a large impact on other personnel involved in a clinical study. Using the previous example, there follows some benefits which the various personnel involved in the clinical trial could see:

Statisticians - The IVR facilitated a reduction in non-evaluable patients being enrolled. It also improved statistical power by enabling better matched treatment groups (using certain methodology). It prevented over-enrolment, recorded the exact dates and times of enrolment (and follow-up events), and helped to provide interim (and more independent) data to Safety Monitoring Committees.

Project Manager - The IVR provided real-time activity tracking, facilitated remote monitoring of CROs performance and provided the information needed to redirect resources precisely where they were needed.

CRA - These can now know exactly when patients have been enrolled, or perhaps as importantly, when a promised patient or batch of patients has not been enrolled. This enables fast problem resolution. Finally, CRAs do not have to spend hours or days phoning sites checking on recruitment status.

Sites - Study sites only received the materials they needed and, assuming the supply chain was reliable, did not run out. Thus, the arrival of huge, unannounced and unanticipated shipments did not occur.

Patients - Complex calculations were made for the site by the system. This removed the chance of error in dosing and therefore improved patient safety.

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