Latest IRT Systems Accelerate Trial Progress and Support Patient Safety

IRT systems are commonly credited with helping to ensure that the right drug gets to the right patient at the right time. This digital side of the supply chain supports drug distribution activities as well as site-level patient interactions. As IRTs have grown more sophisticated in recent years, their automated functions can actually accelerate the drug's journey to market and improve patient safety. These less-known benefits are especially timely as clinical trials are growing more complex (1)—often involving more patients, more sites, and more countries.

Sponsor companies can often manage supplies and drug assignments for very small clinical trials involving a handful of patients without an IRT system. Few, however, would ever attempt to do so for global trials and/or those involving hundreds, much less thousands of patients. The value of IRT systems is well known in projecting patient demand, managing product expirations, preventing stock-outs, automating drug assignments, and protecting blinded information. Less recognised, though, is the fact that the newer, more sophisticated IRT systems have added features and functionality that address the two overarching goals that sponsors have for their trials: ensuring patient safety and speeding time to approval.

Ensuring Patient Safety

Minimising Human Error

IRT systems are the backbone of medication-related functions within a trial, encompassing:

- Patient screening/rescreening;
- Run-in phase registration;
- Screen failure reporting;
- Randomisation/enrolment;
- End of study reporting;
- Unblinding;
- Medication reorder/replacement; and
- Tracking the status of medications.

IRT systems are validated against the sponsor's requirements, guiding end users along a pre-determined workflow in each of these functions, allowing them to simply follow the on-screen steps as they complete transactions. This prevents users from skipping necessary steps or performing them out of order—issues that could compromise both patient safety and the integrity of study data. Modern IRT systems also have built-in business logic that is defined by the needs of the particular trial, but in general, it is designed to minimise the amount of manual intervention in study-critical points such as randomisation and dispensing. For example, an IRT's business logic can:

- Perform dosing calculations, which helps take the onus off of site pharmacists to ensure that doses are administered in the correct volume and concentration;
- Prevent data from being entered that falls outside of acceptable parameters or that is in the wrong format; and
- Ensure that critical fields are completed so that a patient's participation need not be invalidated for lack of critical information.

This business logic can be especially important in trials involving hundreds of sites across multiple countries. The IRT, if designed well, can provide an intuitive interface that encourages consistency while decreasing the need for extensive, costly, and time-consuming site training. While an IRT cannot prevent all human errors in study administration (someone could still enter the wrong information or do something incorrect with the information the system provides), it can minimise the opportunity for human error and increase the detectability of any errors made. In the event that erroneous data did make its way into the system, the IRT provides an audit trail of any data corrections performed.

Monitoring Adverse Events

Traditionally, sponsor companies have captured reports of adverse events (AEs) through the electronic case report form (eCRF) that investigators complete during patient visits, and the details are collected via the electronic data capture (EDC) system.

What many progressive companies are now discovering is that all of the same functionality within the IRT that is used to monitor and control trial progress towards milestones (such as screening, enrolment, and randomisations) can be leveraged to monitor AEs. When a patient discontinues trial participation, the investigator records this fact in the IRT, and increasingly, sponsors are requiring that investigators use the available fields to indicate the reason for discontinuation. Often the reason is related to an AE. Similarly, any unblinding events (which are almost always indicative of AEs) are recorded in the IRT. Very likely, the notification of the unblinding event would be received before the details in a completed eCRF.

The IRT supports near real-time monitoring (in the best systems, data are refreshed multiple times a day), which is important both in terms of immediately identifying events that may be relevant to patient safety and for complying with regulators' timelines. (The US Food and Drug Administration (FDA) requires notification within 15 calendar days for AEs and within seven calendar days for serious AEs.)

And, rather than having to go in search of the

information, trial monitors can be automatically notified when the system registers a patient discontinuation or an unblinding event, or when the number of such instances reaches a pre-defined threshold. Sophisticated IRTs can accommodate "transaction-based alerts" that are set to notify trial monitors based on certain triggers. Thresholds can be defined by site, country, study, or treatment so that study monitors can initiate investigations when and where needed.

Speeding Time to Approval

Accelerated Data Submission

Some IRTs are capable of providing information in the specific format needed for submission to regulators. They convert the database through a valid transformation process into any structure required, such as what is outlined in the Study Data Tabulation Model (SDTM), for example. (The SDTM is part of the Clinical Data Acquisition Standards Harmonization (CDASH) Standard.) This means that when the study closes, the data captured in the IRT are ready to go, without needing to be reformatted—which can be a protracted process.

Another benefit of newer IRTs is that they allow for interim analyses of safety and efficacy at any point in the course of the trial; the data export is always ready. This is particularly helpful for products receiving breakthrough therapy or fast track designations in which the FDA conducts rolling reviews of marketing application materials.

Automated Accountability, Reconciliation, Returns, and Destruction

The trial administration process can also be shortened when IRT systems extend to accounting for supplies from their manufacture until they are either consumed by the patient or destroyed. Regulatory agencies around the world mandate that sponsors be able to prove that study medications were administered only to the correct patients and according to the protocol. As drugs move through the trial, the following documentation must be kept:

- Site personnel must maintain logs when they receive drugs from depots, dispense them to patients, or accept them as returns from patients;
- Clinical monitors must verify that the logs for all received, utilised, and returned drugs at each site match the physical quantities and status of materials;
- Monitors must maintain a record of any returned drugs to a collection destination; and
- Sponsors must receive a certificate that identifies and quantifies any drugs that were shipped to a designated destruction facility and destroyed.

Any discrepancies identified must be investigated, explained, and resolved in order to fulfill regulatory requirements and support the study findings. When sponsors rely on a paper-based system to track the disposition of supplies, they typically have to contend with disparate and/or duplicate entries. And, because the information is recorded in many formats, it can be difficult to consolidate for reporting and analysis. Often, study teams spend as much time verifying and correcting logs as it took to perform the actual accountability and reconciliation functions in the first place.

An automated system that is an extension of the IRT, in contrast, reduces errors through logic checks and using drop-down selections rather than free text, notifies monitors of discrepancies as they happen, supports real-time queries as to the status of drugs, and allows for reporting to auditors at any point in time. These capabilities vastly improve the efficiency of drug supply management and shorten the trial administration process. Users have an opportunity to resolve issues as they arise, rather having to deal with them *en masse* prior to study close.

Avoidance of Delays from Stock-outs

IRT systems play an integral role in managing medicines during trials, including the assignment of kits, ordering of drugs for sites, managing product expiration dates, and tracking the inventory of products as described above. With an IRT system, site inventory levels are tracked in real

Poor Resupply Strategy Leads to Patient Loss… Potential Trial Delays

The sponsor of a Phase III trial spanning more than 700 sites in 49 countries was experiencing a high rate of "insufficient product alerts" in the company's IRT system. In one year, 838 patients—between two and three a day—were being turned away at sites because there wasn't enough of the right dose strength in the right country at the right time to meet patient demand. This situation had the potential to extend the timeframe of the trial significantly.

The issue was that the resupply strategy was not synched with actual patient demand, and frustration was mounting at clinical sites as well as within the sponsor's operations team. An inordinate number of patients were leaving the study and enrolling in competing trials, of which there were many.

The solution was to prepare a new forecast and resupply strategy based on real-time updates on patient enrolment, product usage, and expiry dates.

Over time, as the sponsor's product production "caught up" with the more accurate forecast, the rate of insufficient product alerts dropped sharply from its high of 4.7 per cent to a reasonable 0.2 per cent, patient discontinuations decreased dramatically, and complaint calls from sites dropped in equal measure.

time, and resupply orders are automatically generated when the inventory level at the site reaches a minimum value. In addition, reset values can be configured to initiate alerts when the inventory at a site or depot reaches a critically low level or when products are about to expire. This helps to ensure that proactive measures are performed to reduce the likelihood of a stock-out.

Also over the course of a study, the initial baseline forecast is continuously refreshed based on real-time updates of what is happening with patient enrolment and product inventory as reported in the IRT. Supply chain managers, alerted to variances from the baseline forecast, can modify the forecast and know with great precision how much drug to produce and when. Such dynamic management aids with budget preparation, prevents the wastage that comes from stockpiling supplies, avoids the risk of stock-outs, and reduces emergency measures needed to replace expiring drugs.

Without this virtuous cycle of information, companies can easily get caught with insufficient supplies to continue enrolment or even to follow the treatment regimen for enrolled patients, given that the lead-time to get products through the manufacturing, packaging, labelling, and distribution cycle can be many months. There have been instances in which poor inventory planning has led to stock-outs that forced sites to delay patient recruitment by many months.

The automated tasks performed by an IRT system obviously create efficiencies throughout the clinical trial supply chain, but less obvious is how these efficiencies can speed a trial's progress toward closure and how the checks and balances built into an IRT can improve patient safety. The features and functions of the most sophisticated IRTs minimise human error (especially at critical junctures such as randomisation and drug assignment), provide real-time monitoring of AEs, speed the preparation of data for submission, and prevent stock-outs that lead to patient loss and trial delays.

References

1. http://www.businesswire.com/news/home/20150130005621/en/Research-Markets-2015-Trends-Global-Clinical-Development, visited on December 29, 2016.

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