

Pharmaceutical Executive



In *Search* of the Holy Grail

*Chasing ultimate clinical trial efficiency,
one small step at a time.*

BY ROB CASE

MOST PHARMA COMPANIES, INCLUDING PROCTER & GAMBLE PHARMACEUTICALS (P&GP), rely on a familiar line-up of information technology solutions to shorten clinical trials timelines, manage data and contain costs. Clinical data management systems (CDMS), clinical trial management systems (CTMS), electronic data capture (EDC), drug supply management (DSM), and interactive voice-response systems (IVRS)—all of these have become commonplace. Widely touted logistical and commercial benefits helped drive the rapid adoption of such programs in clinical studies around the world. And while companies like P&GP have reaped enormous benefits after implementing these programs,

they all see a greater, unrealized upside shortly after implementation. These IT solutions would be much more powerful if they worked well together. But almost invariably they do not. What would it take to integrate the data so that each system could share information with its neighbors?

Unfortunately, building bridges between such systems is not easy. Even though the different programs use common data points and trial metrics, few of them permit data to flow smoothly from one to the next. Instead of monitoring a network of programs that update one another automatically, sponsors and site managers must devote hours every day to keeping the different systems in sync. To avoid these costs, P&GP set out to eliminate double work and extra steps like duplicate data entry and the time spent finding and correcting the errors that inevitably result. It turned out to be a tricky process, one that proceeded stepwise, a little at a time, and served up a few surprises along the way.

In the Beginning

By 2002, P&GP had successfully implemented several systems to manage clinical trials and capture data electronically. Looking for ways to share common data, trial metrics, and so on, the company called on its vendors for help implementing the vision. Management identified three systems for initial integration: interactive voice and Web response (IVR and IWR), EDC and, later, the CTMS. The suppliers for these systems also recognized the value of sharing data between their systems. P&GP used ClinPhone's IVR and IWR for randomization and management of trial supplies, and also relied on ClinPhone's IVR system for the collection of patient diaries. The EDC system is Phase Forward's InForm™. More recently, the company began using Perceptive Informatics IMPACT application to aid the overall management of clinical programs.

Data integration turned out to be a high-stakes game. Four out of five studies take longer than expected, and issues at study sites account for almost 60 percent of these delays. ClinPhone estimates that keeping a trial running costs around \$40,000 a day, while the impact on lost sales revenue is even more pronounced. Every extra day that a drug remains in clinical studies costs the sponsor at least \$600,000 in lost sales. For a potential blockbuster, the daily revenue lost could reach eight million dollars.

Some of these costs can be traced to sheer excess optimism. "Investigators overestimate the pool of available patients who meet inclusion criteria and who are willing to participate in clinical research," says Louis Lasagna of Tufts University, summing up part of the problem.

But unnecessary steps in a trial process, or pointless duplication of documentary data, also contribute to the rising costs of clinical studies. Data integration could reduce the toll these costs take on clinical budgets. The

quest for a solution begins with the fact that many IT systems used in clinical studies have common data points. For example, patient demographics might reside in several systems. An investigative site coordinator may enter patient demographics using the IVR database and later enter the same information into an EDC system. When cleaning data prior to locking databases, any data-entry errors or discrepancies between the two systems must be resolved. Of course, this takes time and resources. Integrated solutions would eliminate redundant steps—such as re-entering data. Sponsors could cut costs and save time. Equally important, they would reduce the risk of data entry errors.

P&GP chose to pursue seamless and bi-directional integration. That is, we wanted data to flow in two directions: from the electronic case report form (eCRF) to the CTMS and vice versa. We wanted a system designed to improve data reliability, to enable managers to track progress, and to allow operational applications and analytical applications in various departments to use the data. In theory, such data integration could be relatively straightforward. After all, the same data is used in different departments across the company. Unfortunately, those different departments use IT systems from different vendors, who in turn use a variety of incompatible data sources, applications and channels. Everyone may use the same data, but most users are stuck with the data in their own system.

An Incremental Approach

P&GP took an incremental, evolutionary approach to data integration. One at a time, we added systems to the current integrated network, assessed the results, and applied the lessons learned to the next integration. Each integration represented a landmark on a road map sketched out in advance. Each step was planned to reach the next landmark. Moreover, each addition to the integrated network is implemented first as a pilot project, and later as a full-scale implementation.

The company began by integrating Phase Forward's InForm™ EDC and ClinPhone's IVR system. In the first study, only a few data points were integrated, mainly those dealing with demographics and randomization. After achieving this limited integration and recognizing the benefits, P&GP added other elements into the mix, including IVR diary data. So far, integrated diary data collection has only been used on two trials at P&GP, but the benefits were dramatic enough to



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make it a candidate for future trials as well. The successful integration of these two systems from different vendors underscores that integration can work as long as the vendor companies have the technology and personnel to support the venture. Effective integrations require an active partnership between vendor and client.

P&GP discovered that a network resulting from even a modest integration offered benefits that exceeded the sum of its parts. For example, patients registered in ClinPhone's IVR database were enrolled in InForm automatically. Within minutes, site personnel were able to use the EDC system to enter clinical data. Moreover, patient diary data collected using ClinPhone's Patient Direct automatically populated the eCRFs in the InForm system. This enabled real-time evaluation of diary data at each site. In addition to showing mission-critical data, such as protocol adherence and recruitment, real-time evaluation helps monitors to identify safety issues earlier than they could had they used non-integrated systems.

Patient screening and enrollment reveal additional benefits of EDC/IVR integration. Before the two systems were integrated, site coordinators created a case book, which they populated with patient data. The integrated system uses IVR for screening and enrollment. Now, by the time a site coordinator logs into InForm, IVR data

monitor the systems and take corrective actions. The company worked at keeping the system architecture straightforward, avoiding needless complexities. For example, a "data ownership" rule made certain that a data item originating in any given system could only be changed in that system and not in any other. The change would then roll through to the integrated databases. Simple guidelines, such as the data-ownership rule, help simplify procedures for troubleshooting the systems.

Of course, no one could anticipate every problematic scenario. The benefits of sharing screening-log data came with an unexpected downside. Like most drug companies, P&GP is increasingly focused on timely patient recruitment for clinical studies. In particular, investigators became interested in why patients fail screening. When



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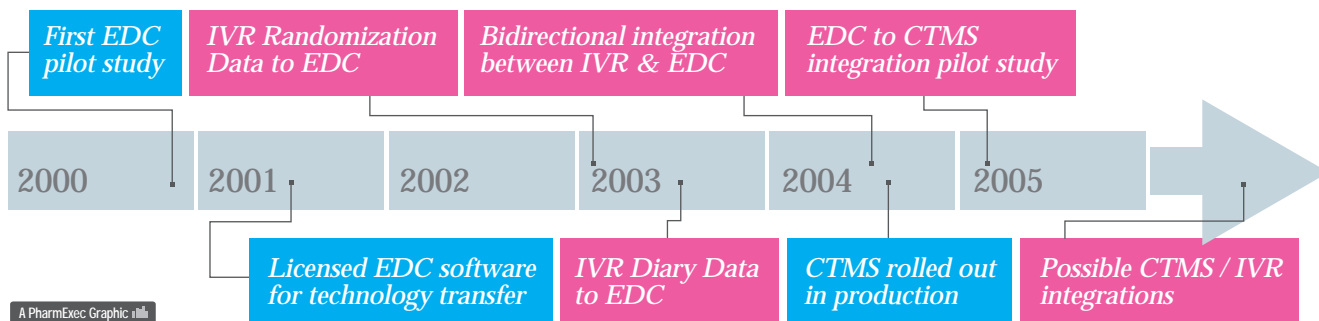
P&GP eClinical System Evolution

key

Integration

New Technology

Since January 2003, IVR/EDC integrations were implemented on 100 percent of P&GP's Phase II/Phase III clinical trials (excluding ongoing and extension studies).



has already populated the case books for newly enrolled patients. The coordinator can begin data entry immediately. This reduces the workload on clinicians, who do not have to transcribe diary data, calculate scores, or enter screening and demography information twice. The integrated platform enables clinical trial sites to take full advantage of each solution's capabilities, while eliminating duplication. Furthermore, integration reduces the length of our IVR calls, simplifies EDC entry, and allows investigators to view the data in real time. Moreover, entering the data only once reduces the risk of discrepancies that can occur whenever the same piece of information is entered into more than one system. The data management team must no longer look for—or query—discrepancies between two systems. Depending on the number of patients enrolled, eliminating data discrepancies could save days of effort in each study.

When planning such integrations, P&GP built in quality controls to

analyzing screening patterns, we found that data-entry mistakes were relatively common. In some cases, a screening failure was inadvertently enrolled in the study. In others, a volunteer who met the inclusion and exclusion criteria and who had signed informed consent was excluded in error. By the time the error was discovered, the EDC system contained incorrect patient details and the patient either randomized or excluded. As a result, either the patient needed to be rescreened, or the misattributions had to be reconciled.

Often, this problem emerged only after the investigator called to randomize the patient using IVR. When a patient is mistakenly screen failed,

he or she is not visible in the EDC system, and site personnel cannot enter further clinical data for that patient. As a result, the investigator calls the help desk. From the perspective of the help desk personnel, a patient might fail to appear in the system for several reasons. But nine times in 10, the error arises through data entry. Typically, it takes a member of the help desk staff half a day to identify the cause of the problem, and the rest of the day to fix it. In a study that enrolls four hundred or five hundred patients, such problems may occur, in P&GP's experience, 10 or 15 times. Although the true cost of this additional effort has not been calculated, it is safe to assume that the increased help desk, data cleaning, and monitoring efforts result in significant costs. However, with a few minor adjustments to the integration workflow, such issues can be overcome.

Ironically, one of the IT system's great strengths—real-time updating—contributed to this problem. Investigators invariably are impressed when they use IVR to enroll a patient and, in just a few minutes, look at the eCRF and find the case report form ready. Real-time updating is also impressive when demonstrated to the end-users at the sites. However, P&GP managers are beginning to question whether updating ought to be so rapid. Typically the information is available throughout the integrated system within five minutes of entry into one interface (for instance, the eCRF or IVR). It may turn out that a slower turn around, perhaps batch processing each night, would give investigators the opportunity to catch these mistakes while still allowing timely decision making. On the other hand, lengthening the turnaround time might impede the workflow at the site, especially since investigator time is at premium.

Managers implementing data integration must consider the needs of internal and external stakeholders—patients, investigators, the medical department and the clinical research associates (CRAs)—as well as the technical issues. In general, internal and external stakeholders readily accept data integration. In-house, for example, the integrated network allows the medical department and CRAs to stratify the data; for example, they can analyze the clinical study cohort according to various demographic or inclusion criteria.

Dealing with Pressing Problems

Bidirectional data integration of CTMS and EDC may eventually encourage investigators to participate in clinical studies, particularly those motivated by financial considerations. Investigators understandably want to be paid for their research promptly. At the same time, sponsors want to receive clean data as quickly as possible. This means that sites must not only enter data promptly, but also must respond to queries in a timely manner. Now if CTMS is being used to generate investigator payments based on certain milestones, a logical step might be to transmit metrics on clean case books from the EDC system to the CTMS so that sites can be paid for clean, final data.

Further integrations with CTMS could involve investigative site

addresses, which are already entered and maintained in several systems. If CTMS represents the definitive source for up-to-date site information, then other clinical systems could access necessary names and addresses from this source. Re-entering such information is inefficient and a great time-waster. For example, if an IVR system automates medication resupply to each site, why not allow CTMS to send current address information to the IVR rather than requiring a study-team member to look up and rekey the address? The bidirectional data flow also could ensure that study materials are shipped to study sites in the timeliest manner. For example, if CTMS tracks institutional review board (IRB) approval of a site, that, in turn, could signal the IVR system to ship the initial drug supply to that site.

When discussing integration (or any new technology for that matter) executives often ask for a quantified return on investment (ROI). This currently remains an open question, and one that P&GP integration teams are not focusing on. Some companies claim that their EDC system saved tens of millions of dollars per year. Others say the new systems are cost-neutral compared to their old paper-based systems. For the time being, P&GP is more concerned with accelerating and simplifying processes, reducing the time to lock each study database, and improving overall study management. Nevertheless, the company does aim, eventually, to identify a set of metrics that offers unequivocal evidence of the financial ROI.

A carefully considered approach to data integration can benefit every stakeholder from the investigator to the pharmaceutical executive. Data integration can reveal new nuances for clinical studies, such as why so many patients fail screening, and pose new questions about the dynamics of current workflows. But P&GP is moving forward cautiously, one step at a time. Great haste in the beginning may not be the best way to reach our ultimate goal: commercializing a drug as quickly as possible. As this example illustrates, many of the benefits of data integration are proving to be greater than the sum of their parts. As we continue to develop the network, we expect further unexpected phenomena to emerge. Throughout the data integration process, we've learned to expect the unexpected, both in terms of challenges and dividends. ☐

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