Think **Big**

Pharma is constantly searching for ways to reduce the cost and time of getting a drug to market, and one way is to conduct innovative technology-supported, global clinical trials that harness the power of real-time data and insight

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Pharmaceutical, medical device and diagnostics development has become painfully expensive. For the five new AstraZeneca drugs approved between 2007 and 2011, the total cost for each was approximately $11.7 billion – calculated as the total R&D spend in that time, divided by the five drugs. The corresponding GlaxoSmithKline number was $8.1 billion for each of its 10 new drugs approved in the same time frame (1). Ways to shorten the time of getting a drug to market, while also reducing cost, are constantly being evaluated – and one key approach is to run global trials supported by innovative technology.

Today, an estimated 65 per cent of Food and Drug Administration (FDA) regulated clinical trials are being run outside the US (2). Russia has more doctors per capita than any country, and each must have at least five years of clinical trial experience (3). Argentina has been a pioneer in the inspection of sites, Investigational Review Boards/ Ethics Committees (IRBs/ECs) and contract research organisations (CROs), and Brazil has never had a negative result on an FDA audit (4).

The benefits of running global trials include access to diverse patient populations, the reduction in cost and time to bring a drug or device to market, and the ability to test new products in the countries and regions where they will be sold. A.T. Kearney determined that pharma or biotech clinical trials could be completed six to seven months faster in low-cost countries, compared to domestic markets. This represents significant savings given the enormous amount of time needed to complete all phases of clinical trials before reaching the licensing phase. Kearney's best countries for clinical development included China, Russia and India, based on factors including patient pools, cost efficiency, regulatory conditions, relevant expertise, and infrastructure and environment (5).

Other factors driving the conduct of global clinical trials include the sheer number of trials being run today, the ever-increasing safety bar being raised by regulatory authorities all over the world and their need for additional clinical data. There is increased competition from other sponsors, expiring patents and new trials to address additional indications for approved products.

When preparing to launch any global trial, sponsors need to carefully consider the following challenges:

- Ethics
- Financial or contract issues
- Insurance
- Study start-up
- Clinical supply chain logistics
- Data collection and analysis

Ethics

Running ethical clinical trials on a global scale must be addressed first and foremost. To ensure ethical studies, as Dr Russell Medford of Salutria Pharmaceuticals indicated in *BIOtechNOW*, sponsors must:

- Carry out pharmacovigilance using experts who collect, analyse, follow-up and distribute safety-related information from new drug trials
- Establish data and safety monitoring boards to impartially evaluate safety as studies progress
- Form regular sponsor monitoring of clinical trial sites to ensure quality, compliance and safety of research participants
- Have quality assurance units that audit operations associated with clinical research to ensure adherence of company personnel to regulations, guidelines, and internal and external procedures, policies and programmes (6)

Financial or Contract Issues

In order to get global clinical trials off the ground, contracts with doctors' offices, hospitals and healthcare providers must be established around the world. Many global clinical trials involve hundreds of investigator sites in numerous countries. These contracts cover the clinical trial work and compensation for the services rendered to the patients in the studies. New companies like Clintrax Global of Raleigh, North Carolina, have seen the need for negotiating contracts for the growing number of multinational clinical trials, and have deployed a network of lawyers around the world that negotiate contracts in local languages (7). The company leverages a library of country-specific templates and its customers use their software as a service (SaaS) to monitor contract negations in real-time.

Insurance

Keeping track of the various international insurance requirements can be extremely time-consuming (8) – for instance, India, based on banking and finance law, requires payment of the premium before the coverage goes into effect; and Russia requires a separate per-test subject limit. The insurer must often have a global network of dedicated, local multinational managers, claims and service personnel.

Study Start-up

Regulatory and ethical approvals for study start-up in each country vary. Country-specific requirements for protocol approval include: types of allowable research; post-study access to medications; provisions for standard of care; minimum insurance coverage levels for each enrolled patient; and timing where some governments mandate that contracts be signed with sites before regulatory or IRB/EC submission (9).

Nearly 90 per cent of the world's population lives outside North America and Western/Central Europe. One of the benefits of running studies in low-cost countries such as China, Russia and India is the access to patient populations served by large hospitals which serve significantly more people than the average US site. This makes it easier to identify patients by going to one central hospital location. These patients are in need of modern medications and devices, and are thus more willing to participate in the clinical trial. As with any study, informed consent is mandatory.

It has been noted that the lack of well-translated material that accounts for differences in linguistic, cultural and population demographics is one of the leading causes of trial delays in developing countries (10). Drawing valid scientific conclusions with data from ethnically and culturally diverse populations, multi-lingual translation can have a critical impact on the trial. Lack of well-translated material is one of the main causes of studies not being on time, and can ultimately lead to bioscience companies facing delays in developing a drug or device, which can result in commercial losses of $1 million in sales per day.

Clinical Supply Chain Logistics

In a complex global environment involving country-by-country regulatory compliance, shipping and logistics nuances, depots, supply management, material stability, comparator sourcing and partnering with contractors, it is imperative to be able to perform 'what-if' proactive demand planning scenarios, using a flexible forecasting system (11). The nature of investigational trials involves the constant uncovering of new data, relative to the activity and effects of the medication. The net effect on clinical trial material requirements for one or more global study can often be dramatic, putting stress on the supply chain to react quickly to new demands.

The worst situation would be if a patient were to show up for a scheduled visit in a far-off country, and the drug or device was not available or in poor condition. This could lead to the patient dropping out of the trial, restarting the recruitment process for the patient pool. To avoid this problem, it is imperative that regulatory compliance with the originating and destination countries be understood and followed – including the creation and control of essential documents and study initiation. Some countries require import/export permits or material transfer agreements for drugs, lab kits, equipment, and blood and tissue samples, and this typically involves a separate application which can take up to a month (12).

Data Collection and Analysis

On the clinical systems front, the concept of having an integrated suite of applications for conducting global

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clinical trials is a pipe dream. With some sites using paper to collect case report form (CRF) data, various electronic data capture (EDC) tools to collect figures from various CROs, and systems in different languages, the problems around data collection can become enormous.

As a result, clinical data used for drug, device and diagnostic regulatory approvals in global clinical trials is typically collected from a range of clinical development systems. These can range from various electronic data capture, clinical trial management, safety, interactive voice response and electronic patient-reported outcomes systems, for example. Some of this data will have been collected specifically for the trial, and some will be more generic, coming perhaps from existing patient records. The source systems can range from propriety, all the way to in-house, one-off databases written specifically for a given purpose – some are SaaS, others are deployed on-site.

In order to identify trends in the data, it needs to be analysed across these different source systems. The problem is two-fold:

- The data is typically in silos that cannot be cross-queried, so decisions are made with limited collaboration
- Real-time analysis of data is often beyond the capabilities of the existing systems, meaning that the information showing that a drug or device should fail can be missed for extended periods, during which expensive testing continues

Many existing analytical systems are purpose-built, meaning they require expensive, in-house IT systems and staff, as well as large, professional service organisations. Manual processes are still often employed to cross-correlate the data and can be unreliable, often producing skewed or incorrect results that are near-impossible to audit.

Sponsors conducting global studies need real-time, multi-data access to data in any clinical or non-clinical development system, providing a single source of truth, with event-driven collaboration and full auditability that can be deployed in a matter of days or weeks via a SaaS-based offering.

Global Success

While conducting global clinical trials presents challenges, harnessing the power of real-time data and insights is key to successfully capitalising on the unique benefits of a global trial landscape. Maintaining ethical conduct; ensuring proper contracts and insurance options are in place; effectively starting up studies; making sure the flow of clinical supplies is occurring with no issues; and that the sponsor is able to make meaningful and actionable decisions based on the data from the trials, are all crucial steps. By covering those areas, sponsors will be positioned for successful global studies.

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Rick Morrison is founder and Chief Executive Officer at Comprehend Systems, where he is responsible for the overall direction and management of the company. In 2012, he was named in the *PharmaVOICE 100*, which recognises the 100 most influential people in the life sciences industry. Prior to Comprehend Systems, Rick spent nearly a decade developing clinical analytics tools, including those used by the FDA and top pharmaceutical companies. He holds a Bachelor's degree in Computer Science from Carnegie Mellon University.
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