PEER REVIEWED

Understanding the Challenges Experienced in the Investigator Initiated Study Supply Chain

Investigator initiated studies (IIS) are an integral part of the investigational drug development process and are increasing gradually, year on year, on a global scale. Phase II IIS studies grew 5 per cent between 2015 and 2017, with Phase I IIS studies also recording an annual growth trajectory within the same time period.[1]

These types of trials can play an important role in helping pharmaceutical companies better understand their drugs, along with appropriate application. Typically, smaller and less complex in nature IIS studies, usually initiated and managed by non-pharmaceutical company researchers or collaborative groups, have the potential to improve patient care and contribute towards future therapeutic breakthroughs by generating drug safety and efficacy data in a real-world environment.

For pharmaceutical companies, IIS can be an excellent tool to help drive internal product development strategies. They can also explore new indications for products already on the market or simply be used to conduct medical research. From the investigator's point of view, the motivation to conduct these studies may be to investigate and broaden the use of new treatments for rare diseases or new treatments for underrepresented patient populations. There is also a drive for investigators to publish new findings and gain recognition for their research.

However, it is not enough to only acknowledge the potential benefit these programmes can deliver. To enable patient enrolment and maximise the opportunity for positive outcomes, it is necessary to scrutinise the indisputable additional challenges these studies can bring. It is then crucial to develop effective strategies to overcome them.

The clinical supply chain contains several risk hot spots for IIS trial managers with multiple functions to organise – from contracts to logistics, kit design and labelling, to inventory management and regulatory compliance. Without clearly defined roles and responsibilities, effective planning and communication, and a clear view of trial data, the potential benefit of IIS programmes can be lost.

So, what are the key considerations when managing investigational medicinal product (IMP) supplies for IIS programmes? And how should clinical supply chains be approached and managed to reduce risk and ensure continuous patient resupply throughout the lifetime of the trial?

Operating at a Disadvantage

Developing and securing approval for a new drug is estimated to cost pharmaceutical companies $2.6 billion, according to the Tufts Center for the Study of Drug Development[2].

In company-sponsored studies, pharmaceutical organisations rely on their Goliathan resource and budget to employ specialist teams. Experienced clinical teams create the clinical trial protocol and manage associated sites. Data management experts utilise the latest technology to generate reports and conduct statistical analysis to identify trends, anticipate risk and continuously harmonise recruitment predictions with supply forecasts. Compliance is managed with regulatory submissions from specialists. Supplies – the coordination of bulk material, as well as clinical packaging and labelling functions – are managed by a highly skilled team of people. Finally, vendor

managers liaise between departments and third parties to proactively seek out opportunities for continuous process improvement.

Despite these resources, on occasion, challenges can occur. Unpredictable events can influence enrolment, which in turn can quickly lead to overage and waste, or a shortfall in supply, negatively impacting the patient. Equally, unavoidable mid-study protocol changes can lead to delays and require prompt and accurate mitigation. However, with experience, technology and specialist vendors in place, situations can be managed, and disaster averted.

In contrast, IIS programmes have little resource to harness therefore operate at an immediate disadvantage in comparison. Investigators are required to assume responsibility for all the pre-mentioned functions and the myriad of tasks associated with them. In doing so, they can spread themselves thinly over a vast remit which, in turn, can compromise the study's ability to provide the right drug, to the right patient, at the right time. As such, IIS trials tend to progress at a slower pace than company-sponsored trials while investigators essentially 'learn on the job'. Although some IIS models benefit from extensive involvement from the pharmaceutical company, the majority operate in relative isolation.

Breaking Down the Challenges

The benefits of running IIS trials are often offset by the multiple challenges synonymous with physician-led

programmes[3]. The three core supply chain challenges evident in IIS trials relate to roles and responsibilities, inexperience in managing clinical trials and a lack of data visibility.

Clinical trials management usually has not formed part of an investigator's remit prior to embarking upon an IIS programme. They are key opinion leaders in their own field but may not have had the exposure to all aspects of running a clinical trial. The level of support offered to them, when their proposal for an IIS is approved by the pharma company, will vary from company to company. With just the one clinical site to cater for, at face value the process of ordering IMP from the pharmaceutical company and dosing patients at site can seem straightforward. It isn't. It is a live, reactive, multifaceted entity where one overlooked element can cause a ripple effect, introducing unnecessary risk and lengthening timelines.

Through in-depth research, peer support and holistic and strategic planning at the earliest opportunity prior to the study's inception, this challenge can be met. Using standardised templates for contracts and agreements between investigators and pharma companies or CMOs will help to determine roles and responsibilities. They will ensure thorough understanding of processes creating greater agility and flexibility which, in turn, helps to reduce study start-up time, costs and risks.

This lack of awareness of roles and responsibilities is understandable and stems from a general inexperience in managing clinical trials. From a clinical

supplies perspective this can, at times, translate into too much inventory being ordered, which can lead to waste due to IMP expiry. Additionally, requests for supplies can often be left to the last minute, due to a lack of understanding of the tasks and timelines involved.

Effective clinical trials management is also reliant upon clear visibility of trial data. Although the scale is smaller, the principles remain the same. However, IIS trials rarely have access to a centralised data capture system. This can make it more difficult to see where patients are in the trial, which can impact forecasting activities. Investigators can over-estimate the recruitment rate for the trial which can result in an extension in the trial timelines. This significantly impacts the supply chain when considering product expiries and the knock-on effect of additional packaging activities.

Centralising the IMP management of IIS programmes with a single group to focus expertise and streamline processes will help to generate a reliable forecast and help to set achievable milestones. Replacing manual ordering and drug assignment with randomisation and trial management systems such as interactive response technology (IRT) will give the investigator full visibility of patient activity and IMP usage in order to help them make clear, informed decisions. It is also worth noting that many vendors offer simplified systems for randomisation and / or inventory management. These systems may have less functionality than a full IRT; however, they can be a much more cost-effective solution and may be especially suited to IIS programmes. If the technology is set up and maintained in conjunction with an experienced supplies manager, it offers greater reassurance that inventory management at site is taken care of.

Building the Strategy for a Patient-focused IMP Supply Chain

Haven taken a look at the challenges that can come with an IIS trial, there are several core areas within the IMP supply chain for IIS trial managers to focus on in order to design an effective and patient-focused strategy.

Where contracts are concerned, physicians need to be aware of what they are accountable for. Not only do physicians need to dedicate time to understanding their responsibilities, they also need to familiarise themselves with contract templates and identify what activities need to be outsourced.

The importance of kit design is something which can easily be overlooked. To reduce the likelihood of getting it wrong, physicians should contemplate the multiple factors that influence design far in advance of production. Factors such as visit duration, dose per visit, visit windows,

the end user, compliance and product stability all need to be considered to produce an end product that is fit for purpose. The same is true of clinical labelling, which becomes even more complex for IIS trial managers running multi-country trials. Despite limited exposure to the intricacies of clinical labelling or knowledge of the lengthy timelines involved, physicians will need to bring the CRO/CMO on board to assist with Master English Label Text (MELT) generation, regulatory review and translations.

Documents needed for quality release can be either study- or product-specific – something which the physician may not have had exposure to. Similar to contracts, uncertainty here can cause serious delays, if the physician is unaware of who to request this information from and fails to do so in a timely manner.

It is possible for IIS trials to co-ordinate forecasting and inventory management independently. However, this is a vital component which demands time and strategic planning to get right. Physicians have a choice to either contract this activity out to CMOs or dedicate significant time and resource to analysing data – relating to expiries, bulk availability and recruitment rates – to determine accurate supply.

The same is true of logistics. It's not enough to understand the timelines and specific country requirements relating to import and export, the physician will need to demonstrate full traceability for the drug from production to storage and distribution through to returns and destruction. This requires comprehending the associated processes and access to systems to gather the necessary data. In practice, however, very few physicians have previous experience of these systems, such as interactive response technology (IRT), and in addition, there often isn't the budget available to purchase them.

Conclusion

To keep patients, their safety and experience at the heart of IIS trials, investigators need to define the IMP supply strategy at the earliest opportunity. By establishing which activities need to take place, and by understanding the interlinked nature of supply and demand, IIS trial managers would be better placed to identify risk and make informed decisions about what they can and cannot manage. They will also gain a clearer idea of what should be outsourced to expert vendors with access to the people, processes and technology needed to deliver a successful IMP supply chain operation. By championing clear and consistent communication with these vendors, and providing regular updates on study status and changes, all challenges can be managed, and a streamlined, cost-effective, patient-focused IMP supply chain successfully established.

REFERENCES

1. Source: GlobalData: Total Investigator Initiated Clinical Trials from 2015 forwards across all geographies; includes ongoing and planned studies by phase of development.
2. https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176691/

Victoria Maguire

Victoria Maguire, Project Group Manager – Supply Chain Management Vicki Maguire graduated from Aberdeen University, Scotland, with a MSc in Sports Nutrition. Vicki Joined Almac in 2007 as an IRT Project Manager and has been a member of the Supply Chain Management team since 2010. The team are responsible for forecasting, production planning and inventory management of clinical trial material. Vicki has over 15 years' experience in the Clinical Research Industry, including roles in Clinical Study Management and Clinical Pharmacy and has a thorough working knowledge of GMP, GCP and GDP.