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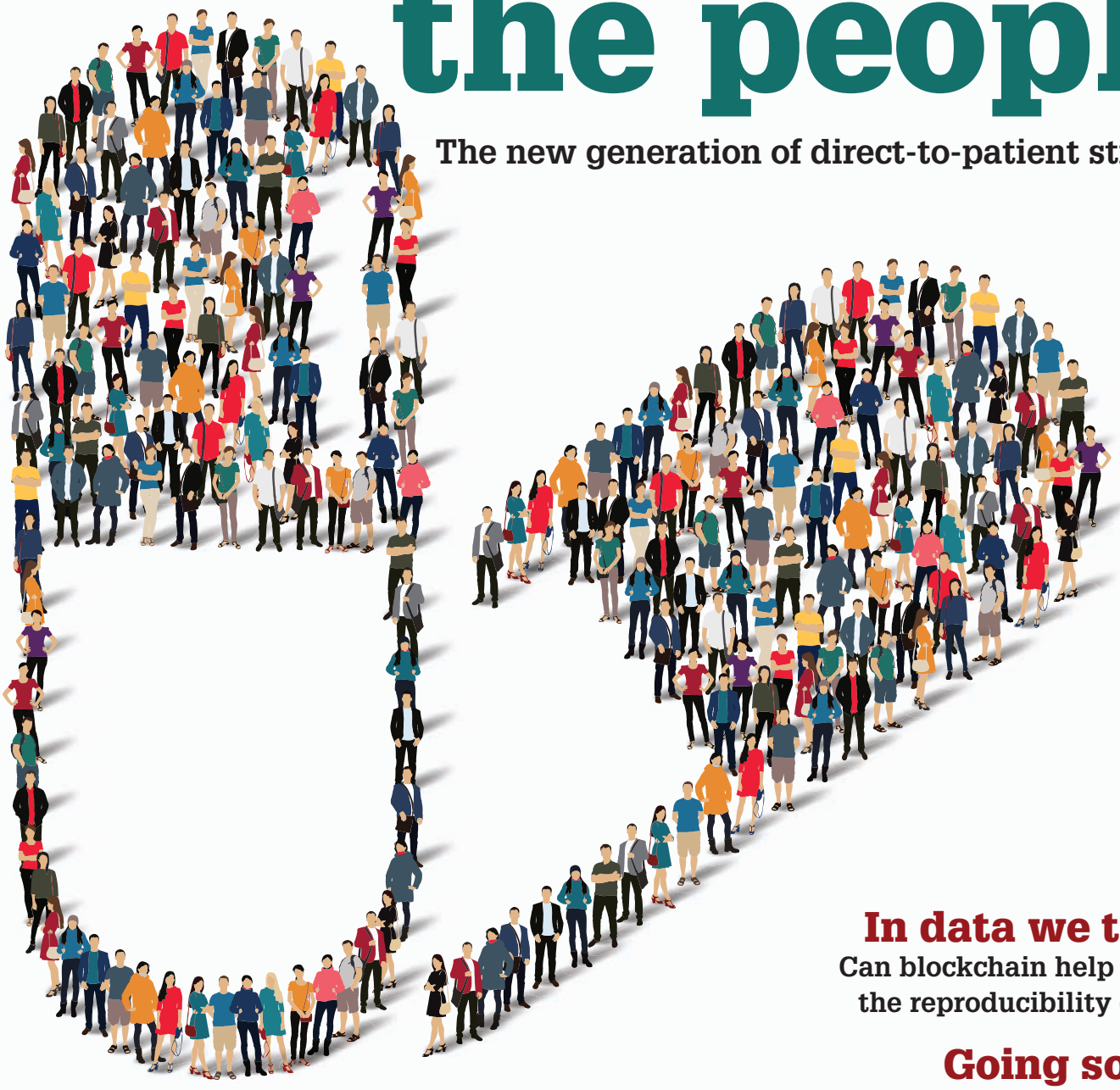

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Editor

Change is the only constant

With the UK rapidly hurtling towards 'Brexit day', the Clinical Trials Regulation due to be implemented in 2019, ongoing technological advances and a simultaneous drive for 'patient centricity', the face of clinical trials is dramatically changing.

A number of opportunities are provided by these developments. New regulatory systems provide the ability to speed up approval processes and enhance communication between sponsors, national authorities and ethics committees. The usefulness of technology, such as digitisation, blockchain and clinical data management systems, holds the potential to improve efficiencies along the supply chain and manage the wealth of data generated from trials. Embracing patient centricity can enhance patient recruitment and retention in the short and long term, as well as reducing costs.

Although seemingly incompatible, technology provides an enhanced ability to deliver on patient centricity. It offers new, richer, more convenient and potentially more accurate sources of data, which can be used to improve both clinical trial processes and the experience for patients.

Of course, the challenges of integrating these changes into current practices are very real and require some difficult but important conversations between industry, regulators and patients. As the new editor of *Clinical Trials Insight*, I am hugely excited to stimulate these important discussions both in the current issue and going forwards. With a keen interest in the ongoing developments within clinical trials, combined with a long-standing passion for the central role of publications – such as ours – in being at the forefront of these important dialogues, it is a responsibility I do not take lightly.

Under my watch, I will ensure that every single edition combines analysis of current and future developments with insights from the industry's key figures to provide innovative solutions, helping readers improve efficiencies while minimising costs in all aspects of clinical trials. I hope you enjoy this issue and I look forward to meeting with many of our readers to conduct these exciting discussions in person. In the meantime, I'd welcome your feedback on this issue and your ideas for future editions.

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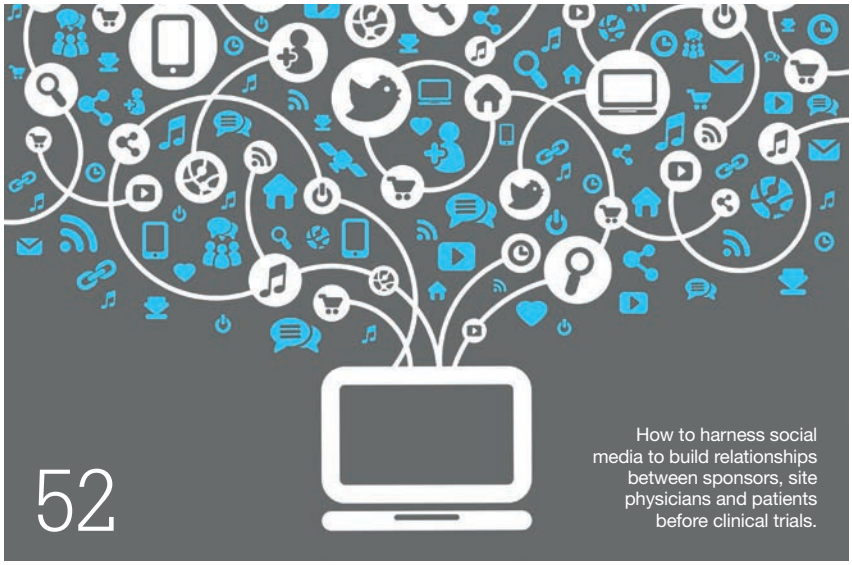
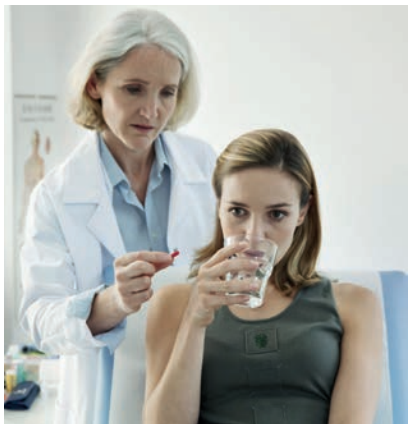


RECRUITMENT

Perception of trials hinders participation

Patients, their families and friends all see clinical trial research as important, but perceive participation as being burdensome, a recent study suggests. The Centre for Information and Study on Clinical Research Participation (CISCRP), an independent non-profit organisation based in Boston, surveyed more than 12,000 people across 68 countries about their perceptions and experiences of trials.

Around 85% of respondents believed clinical research was critical for developing new drugs and 90% considered involvement to be safe, but only 18% had previously participated. The low uptake is perhaps unsurprising, given that almost half reported that trials were rarely discussed with physicians. However, almost 95% felt that physicians should be informed about studies happening in the local community. Furthermore, over 90% were happy with their medical records being used to identify suitable clinical trials collaboratively with their physician. The majority of respondents were also most comfortable with hearing opportunities from their physician rather than an alternative source. This was especially true for older individuals.



Almost half of respondents reported that trials were rarely discussed with physicians.

Among the 10% of participants perceiving trials to be unsafe, primary concerns included the risk of adverse events and a distrust of pharmaceutical companies. Of those who had positive perceptions of involvement, altruistic reasons were the main driver, including a desire to advance science and helping others. Interestingly, respondents also underestimated the time taken to bring a drug to market. Despite taking an average of 12 years, around 40% believed the entire process to take less than five years.

For those who had previously participated in a trial, the vast majority had a positive experience. Over half felt that they received a higher standard of care than usual. More than 90% expressed a willingness for future involvement, with a similar number also inclined to recommend participation to others. However, almost half considered the experience to have been disruptive to their daily routine, particularly younger individuals and those from minority groups. Around 90% of respondents who had been involved wished to receive a summary of trial findings, but just over half had actually been provided with them. Over 70% were also keen to receive their individual results.

As this survey was conducted online and used convenience sampling, rather than randomly selecting participants, results may not be representative of all patients. Nevertheless, these findings provide important food for thought about how to achieve and maintain a high level of patient engagement in clinical trials.

REPORTING

Calls for greater transparency

Clinical research has been shaken by the recent findings from the Evidence-Based Medicine (EBM) DataLab at the University of Oxford. EU guidelines stipulate that sponsors recorded on the EU Clinical Trials Register should upload all results within one year of study completion, with penalties threatened for those failing to comply. However, the findings, published in the *British Medical Journal*, revealed that almost half of trials conducted within the EU failed to publish their results.

The lack of transparency opens the door to a number of serious consequences, including compromising the integrity of clinical decision-making and threatening the public trust in the pharmaceutical industry. "This problem strikes to the heart of evidence-based medicine," said Dr Ben Goldacre, director of the DataLab at the University of Oxford. "We cannot make informed choices about which treatments work best, as doctors and patients, unless all results are reported."

With the new EU Clinical Trials Regulation coming into force next year, it is hugely important for companies to respond quickly. "It will bring substantial financial penalties for sponsors in breach of reporting requirements," Goldacre warns.

Perhaps the most concerning aspect of these findings is that they were not surprising to those close to the industry. "Lack of transparency of clinical trials is not a new phenomenon, but rather something that has received unfortunately limited attention," notes Sarah Steingruber, programme manager at Transparency International's Pharmaceuticals & Healthcare division. "The findings from the EBM DataLab are important and quantify the scale of the problem."

However, this is not only an issue for future trials. "The report is very clear – there is urgent need to increase transparency across the research and development process, not only for those trials going forward, but also retrospectively for trials that have already completed," says Steingruber. "The medicines and devices of tomorrow were tested in the trials of yesterday, and in order to truly understand their safety and efficacy profiles, and guarantee that healthcare professionals are able to make decisions that are in patients' best interests, we need that data to be available."

TRIAL DESIGN

Gender under-representation in cardiovascular disease trials

Contrary to popular belief, cardiovascular disease is the most common cause of death for women worldwide.

Cardiovascular disease is the most common cause of death globally for both men and women. However, it is often overlooked as being an important female health issue. This is due to the misconception that females are biologically protected against cardiovascular disease and the fact that the disease tends to develop seven to ten years later in women than men.

The lack of recognition of the prevalence of heart disease in females has led to less aggressive treatment strategies and a lower representation of women in clinical trials. The latter was confirmed in a study published earlier this year in the *Journal of the American College of Cardiology*. The research looked at 57 trials that took place between January 2005 and September 2015, which led to 36 FDA approvals for 35 drugs.

Estimates for the representation of women in trials were calculated by dividing the percentage of women among trial participants by the percentage of women in the disease population, with a range between 0.8 and 1.2 reflecting proportional representation.

The ratio for atrial fibrillation was 0.8–1.1, 0.9 for hypertension and 1.4 for pulmonary arterial hypertension, which were all within or above the desirable range. However, the study found that women were under-represented in clinical trials for heart failure, coronary artery disease and acute coronary syndrome, at ratios between 0.5–0.6. Researchers also investigated gender differences in efficacy or safety, but found little indication of clinically meaningful differences. This demonstrates that treatment effectiveness does not differ between genders.

The paper showed that the enrolment rate of women reflects the lower number referred for pre-trial screening. This could be due to a lack of identification of females as suitable candidates, or their unwillingness or inability to participate. "Based on this, future research is needed to identify factors leading to under-participation of women in cardiovascular clinical trials, particularly those occurring before screening," says Pamela Scott, director of research in the FDA Office of Women's Health.

However, under-representation is not a female-only issue. "Research is needed to better define barriers that limit participation of diverse populations, not only of women but of minority and older populations," explains Scott.

In an accompanying editorial comment, Louise Pilote and Valeria Raparelli emphasise the importance of standing up against disparities. "Patients, researchers and health providers can take action by addressing the alarming gaps in quality and equitable healthcare for women," they write. "Our mandate as health providers and researchers should be to hone the energy and advance awareness that sex and gender in clinical trials really do matter."

REGULATION

Fast track options for trial authorisation

As part of a push to offer patients faster access to new treatments, France's drug regulator, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), has recently established two 'fast track' options to speed up authorisation of clinical trials in the country.

"This new system aims to shorten clinical trial authorisation application processing times, prepare the ANSM for greater responsiveness in view of upcoming European regulations on clinical trials – coming into effect no later than 2020 – and improve the quality and safety of the clinical trials proposed in submitted applications," says the ANSM.

These new routes come in response to the French Government establishing patient access to healthcare innovation as being a key priority at the eighth meeting of the Strategic Council for the Healthcare (CSIS) and being written into the 2018 work plan of the ANSM, the guarantor of the safety and quality of authorised medicines.

Unlike the US Food and Drug Administration (FDA)'s fast track process, which aims to expedite the review of drugs to treat serious conditions and fill an unmet medical need, France's new approach applies only to innovative treatments and known substances. The two routes are called 'Access to innovation' and 'Support for development', which pertain to substances that are new or known, respectively.

Both routes are voluntary and, as of October 2018, are in a test run phase. In using this new system, the ANSM hopes to better prepare applications to meet safety and quality requirements.

The processing times will be reduced to 40 days for new and 25 days for known treatments, which are considerably shorter than the current regulation of 60 days.

Eligibility criterion for known treatments is that a substance or combination of substances have already been evaluated in France for the same purpose as the trial concerned. For new treatments, early-phase trials, paediatric oncology, paediatric haematology and rare disease trials are suitable.

Blockchain: behind the buzzwords

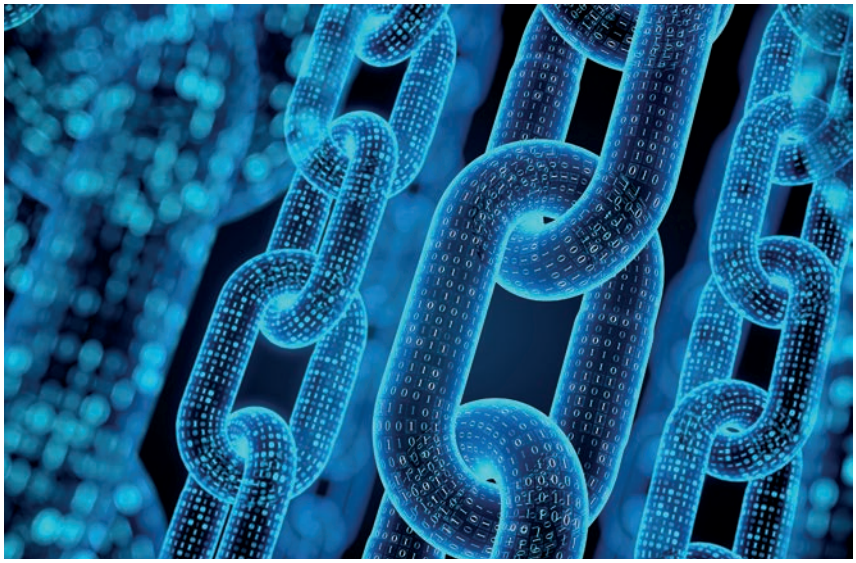
As the hype around blockchain has exploded, its actual applications have become harder to discern. However, specific aspects of the technology have the potential to address the ongoing problem of reproducibility in clinical trials. **Dr Steve Arlington** and **Dr Richard Shute** of the Pistoia Alliance, and epidemiologist and blockchain specialist **Dr Mehdi Benchoufi** tell Tim Gunn what lies beyond the buzzwords.

It sounds almost dystopian, but more people trust the organisations that build their phones than those that take care of their bodies. Across the 28 countries surveyed for communications marketing company Edelman's 2018 Trust Barometer, only 55% of consumers had faith in the pharmaceutical industry to "do what is right". In the US, the world's biggest pharmaceutical market, the rate was 38%, and in Germany, the fourth-largest, a paltry three out of ten people were confident that the sector has patients' best interests at heart.

By contrast, despite the ongoing backlash against election meddling and the way data is used online, three quarters of respondents continued to believe in the moral scruples of technology companies.

Edelman's barometer is a blunt measure, but it reflects real problems. A 2016 study into outcome switching found that just 13% of the clinical trials published in the top five medical journals between October 2015 and January 2016 reported their results correctly. The same year, a survey carried out by *Nature* indicated that more than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have been unable to replicate their own findings.

For Dr Mehdi Benchoufi, a researcher looking for ways to tackle the reproducibility crisis at Hôpital Hôtel-Dieu in Paris, "it's something like a curse".



60% of pharma professionals are thought to be currently using or experimenting with blockchains.

"Poor-quality studies compromise the whole system," he continues. "As a medical professional, you don't necessarily have the time to assess a publication, so you rely on the opinion of your peers. It is very strongly bound to trust."

A question of trust

Appropriately, the most talked-about target for technological disruption is now trust itself.

Blockchain technology, of which the cryptocurrency bitcoin is the most famous example, is "trustless" in that it distributes trust through a whole network rather than relying on a particular guarantor. Of course, trustless isn't quite a synonym for trustworthy, but blockchain is designed to make the distinction moot by automating how contracts are carried out and ensuring that no party can alter information without alerting all the others.

"It means you don't have to rely on a single entity to do the right thing," summarises Benchoufi.

That simple advantage is a powerful draw for the pharmaceutical industry. According to the Pistoia Alliance, a not-for-profit dedicated to supporting innovation in life sciences, 60% of pharma professionals are currently using or experimenting with blockchains, up from only 22% last year. What is more, in 2016 IBM found that clinical trial management was the most popular medical use case for blockchain among healthcare executives.

The statistics reflect something of Pistoia president Dr Steve Arlington's gruffly qualified optimism. As he puts it, "Blockchain gives us an opportunity to build trust levels to a point whereby the first thing a regulator says isn't, 'So, how did they fiddle with this?'"

Arlington stresses the need to be "realistic" about what this technology can do for medicine. Blockchain is not so much a panacea as a type of shared database, and a slow one at that. The key selling point is that it can be directly and safely shared by entities that do not trust each other without relying on a central administrator, but this is paid for by the fact that blockchains are expensive to maintain and hard to upgrade.

Equally, the technology wasn't built with medicine in mind. It was first developed to serve as the public transaction ledger for bitcoin, a digital currency cleared and controlled by a distributed network of computers rather than a central institution. That said, 'trustlessness' might be more relevant to clinical trials than currency. Centralised institutions and middlemen are far better at managing transactions than regulators and publications are at ensuring clinical trials follow the right protocols.

Timestamping using blockchain

In fact, Dr Greg Irving and Dr John Holden of the University of Cambridge have demonstrated that bitcoin itself can be used to unalterably timestamp original clinical trial documentation and automate the process of spotting changes and edits.

It's a far more precise version of tracking criminals with marked money. Like other blockchains, bitcoin uses 'hashes', unique codes of a determined length (in this case 256 characters) that can be created from any form of digital media, to record transactions and attach them to a timestamp. As each block also contains the hash and address of its predecessor, the network continually fingerprints its entire history. This makes it easy to find and check individual transactions, and nearly impossible to falsify them.

Irving and Holden generated a hash from an original clinical protocol, converted it into a bitcoin key, and used that key to transfer bitcoin. This action wrote the key into a block on the chronological chain of hashes and recorded it across the network with a precise timestamp. From here, Irving and Holden showed that any change to the protocol document would be reflected in the fact that any future hash it might generate would differ from the timestamped one on the blockchain.

As Dr Richard Shute, a Pistoia Alliance consultant specialising in blockchain, explains, "You can prove categorically that a specific trial document generated a specific hash at a specific time, and you can be sure that if the data is ever tampered with in the future, the hashing around it will change."

There are a number of applications designed to make bitcoin timestamping easy to do at scale, but using the world's largest digital currency to manage trial data is a bit like holding athletics competitions in the Large Hadron Collider because it's a circuit with good clocks. Benchoufi and Shute both recommend more flexible and fine-tuned blockchain platforms.

Smart contracts

By way of an example, the Ethereum blockchain makes it possible to create non-transactional smart contracts: pieces of code that automate agreements where

trust could traditionally be manipulated, executing as soon as pre-agreed conditions are met.

A method article by Timothy Nugent has shown that a private blockchain consisting of regulators, pharma companies and research associations could implement smart contracts to submit and cement trial protocols, agree and issue trial contracts, manage patient recruitment, read all of the trial data and provide a summary that timestamps every element.

As such, each step (or block) of a clinical trial can be chained together to verify that the designated methodology has been followed, keeping the trial as transparent as possible and preventing any reconstruction or beautification of data.

Shute emphasises the interest the US Food and Drug Administration is showing in leveraging these capabilities.

"If regulators were able to see an entire clinical package with all of its documents traced back through the blockchain," he says, "they could track the trial's history with confidence." The result could be a significant decrease in the time and money necessary to develop a drug.

Nugent's Ethereum method relies on data either being held on-chain or on a shared storage network. By contrast, Irving and Holden only recorded proof of their trial protocol on the blockchain, not the protocol itself.

"That's a critical difference," stresses Shute, "because, given privacy concerns and legal requirements, actually storing personal data on a blockchain, where you cannot remove it, is a big risk. You could just end up with a public database."

Privacy concerns

As secure as it might be, data stored on blockchains and the storage networks linked to them cannot be changed, which means it is likely to fall foul of the EU's General Data Protection Regulation, which enshrines individuals' right to be forgotten.

Nevertheless, at a recent "blockchain bootcamp" hosted by the Pistoia Alliance, members discussed using the permissioned Hyperledger platform to facilitate clinical data sharing with searchable metadata and a blockchain-managed requesting system.

It's an approach already being implemented by healthcare start-ups Timicoin and Medicalchain, which enable patients to finely control and even revoke access to their healthcare data, using Hyperledger to ensure each interaction with it is auditable, transparent and secure. For those organising clinical trials, these initiatives show promise for streamlining recruitment, which currently takes up 30–35% of their budgets, a considerable expense to make sure 20% of trials meet their enrolment deadlines. Shute calls it a "blockchain-enabled dating agency".

It's an interesting comparison. Dating apps store and sell a huge amount of embarrassingly personal information. And if the well-trusted technology industry has taught consumers anything, it's that data, medical or otherwise, is a valuable asset. Blockchain allows patients to take control of it, putting the onus on those running trials to communicate with them effectively.

"Again, it builds trust," says Shute. "There is a risk on individual organisations if they do not adopt blockchain technology in appropriate places. It shows they are not big bad ogres and wolves, but that they're really trying to do the right thing by patients."

That's not to say it's only patients that will benefit. One of the most intriguing applications for blockchain is ensuring the integrity of data recorded by devices like Apple watches and Fitbits through a process similar to timestamping. Shute notes that pharmaceutical companies are still being a little "coy" about how they are implementing the technology, but they certainly have the incentive to do it right.

"I don't know the answers," admits Arlington, "but I do know everything gets much more exciting when you can start using population-sized data." ■

Blockchain has the potential to improve the trust and transparency of clinical trials.

Keep it cool

In a world where supply chains can span multiple national borders, and the regulatory environment is becoming more demanding, good collaboration between partners is essential. Kim Thomas speaks with Sanofi's **Didier Basseras** about how to make it succeed throughout the chain.

Management of supply chains is an increasingly complex process. Regulators demand high quality and reliability, but a lengthy supply chain involving multiple partners across countries makes it harder to ensure that standards are adhered to.

At the same time, drugs need to move quickly and smoothly between sites, with minimal disruption. Biological drugs, which are particularly heat-sensitive and susceptible to contamination, pose tough challenges. So how can pharma companies improve collaboration along the supply chain to minimise process deviations?

Didier Basseras is vice-president global head of clinical supply chain operations at Sanofi, where most of the company's development programmes consist of large molecules that require a storage temperature of 2–8°C.

"When we consider an end-to-end process, cold chain management is still a supply chain challenge," Basseras says. "Drugs being stored and transported at correct temperatures to ensure the quality of the drug at the time of delivery is critical."

The important factors in keeping process deviations to a minimum, Basseras argues, are "maximising the efficiency of cold chain management, reduction of drug transfer and intermediate storage". He goes on to say that a major part of Sanofi's strategy is

"exploring where temperature excursions are happening at investigator sites, while still having robust control of internal manufacturing operations".

But the situation becomes more complex at the investigator site level because a number of sites have limited cold chain capacity.

"We must create an optimised solution early in the process, in terms of volume per treatment and minimising kit void space," Basseras explains. "It's also important to prioritise printing readable labelling information on packaging to facilitate proper use from caregivers – and avoid time that the product is not being refrigerated."

Cold capacity and management are key parameters to assess an investigator site against.

"This good manufacturing practice (GMP) purpose, combined with good clinical practice, equates to one seamless process," Basseras says.

Digital dynamics

When optimising supply chain processes, it's essential to consider the patients' home environment.

"Historically, vaccine refrigeration time has been an important consideration, whereas now we must train patients the proper way to handle new bio drugs," Basseras explains.

Integration of digital tools is helping achieve collaboration across all parties.

"These programmes easily allow information sharing around trials and instructions for drug use," Basseras explains. "Keeping patients connected digitally by using features such as smart packaging also facilitates better compliance."

The regulatory environment is becoming increasingly tough, which means that supply chains need to be completely robust. Visibility and traceability along the whole length of the chain are essential if pharma companies are to be fully compliant. Sanofi has addressed that by integrating digital solutions along the chain to record and act on relevant information.

"Capturing the time out of refrigeration (TOR) is an area where digital is offering dynamic solutions, allowing us to better anticipate when the TOR is expected to exceed what stability allows, and when product replacement will be necessary," says Basseras.

Constantly evolving stability data can create difficulties with the shelf life of drugs.

"To maintain continuity of treatments for all patients requires agility to replace drugs, while also updating the regulatory files to comply with new statements," Basseras explains.

Good organisation of supply chains across countries and sites is imperative, "for either the recovery of drugs we cannot dispense due to the shelf life not covering the full treatment duration, or to facilitate relabelling in the case of an extension", he adds.

These processes must be closely managed with quality and regulatory teams in order to be efficient.

One way of increasing the flexibility of the supply chain, Basseras says, is to have "direct shipping to sites from regional platforms. Proper allocation from one central point to sites in different countries can reduce the quantities needed to cover the clinical demand".

Far from harmonious

This particular allocation model has been successful in Europe's Schengen zone and the US. But it has not yet been implemented in many of the regions where there are political uncertainties, making material flow management across borders more difficult.

The fact that supply chain regulations across countries are still very far from achieving harmonisation is particularly challenging – differing regulatory environments can be a major hurdle to moving clinical supplies successfully between countries.

Nevertheless, the changes that are occurring in emerging markets such as China are sending a strong signal to the rest of the world.

"China is aligning their clinical regulations with other health bodies worldwide, offering Chinese patients the opportunity to receive the most cutting-edge drugs without delay," explains Basseras.

Nonetheless, achieving consistency through all elements of a supply chain isn't easy. While technology plays an important part in improving collaboration between partners, a shared organisational focus is crucial.

"This can be achieved through making supply chain processes more efficient and tailored to the patient's needs, through practices like the direct-to-patient (DtP) model," says Basseras.

This model, he argues, is a good way of ensuring collaboration throughout a supply chain.

"Since its implementation several years ago, the DtP approach is contributing to better patient service, particularly in the case of patients with disabilities," explains Basseras. "DtP cuts down on frequent visits to the pharmacy and physician's office by having the drug delivered directly to the patient."

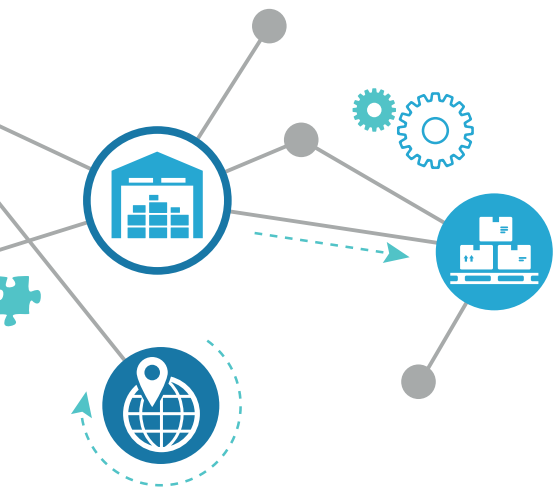
Beyond DtP, he adds, there is an "opportunity to combine drug dispensing with collection of patient samples to be dropped at a central lab".

"This integration of services creates the opportunity for a more efficient supply chain" explains Basseras.

Reverse logistics

Increasingly, pharmaceutical companies make use of outsourcing partners to manage the specialist requirements in the supply chain. Outsourced logistics partners can be a particularly good resource, says Basseras, as they can "offer their expertise for important services like using high-tech shippers for controlled temperature drug delivery, as well as offering digital solutions".

"Because of the high cost of these temperature-controlled shippers, Sanofi is now using a reverse logistic model, which allows the extension of the use of these shippers around the world through different depots."



Beyond the logistics role, Sanofi also uses outsourcing partners that can offer GMP services supported with qualified person for late-stage customisation of treatment kits, mainly for secondary pack labelling and relabelling.

"Their role is greatly contributing to the adaptability and flexibility of the global clinical supply chain," says Basseras.

Like all pharma companies, Sanofi faces the difficulty of predicting demand so that patients receive drugs in a timely manner. Forecasting and managing that demand begins in the clinical trial development stage, says Basseras, "where incorporating technological solutions helps to increase efficiency, from enrolment through data collection and analytics".

The challenge increases in large clinical trials where a single investigational programme may be taking place in hundreds of sites across more than 50 countries. The use of multiple IT systems adds to the complexity.

"The end-to-end track-and-trace challenge involves many companies, from the manufacturing up to the dispensing of the drug," Basseras notes.

This requires major collaboration efforts from quality, procurement and supply chain for Master Service agreements (MSAs) as well as Master Quality agreements (MQAs). However, there are strategies to simplify these processes.

"Reducing the number of vendors across the world by building partnerships is helping to decrease the complexity of the chain of custody with opportunities to limit the number of IT solutions, interfaces and tools," explains Basseras.

Even so, the difficulties of managing inventory when different partners are involved are substantial. Material master data management is a daily challenge in terms of inventory management, both at the hospital level and for all stakeholders along the care chain.

"We have the same number of codes and practices as other large pharma companies that conduct a huge number of trials in the same major hospitals around the world," says Basseras. "This makes securing the correct operation to dispense the right drug even more critical."

A new standard for managing clinical trials

There has been growing discussion in the industry in the past year about the possibilities of adopting the GS1 worldwide clinical trial management standard. Sanofi is one of those pioneering its use. Already, Basseras explains, GS1 is being integrated for use "by the entire chain of personnel in pharma labs" and kick-off is anticipated to occur in the first quarter of next year.

Over the last two years, Sanofi Clinical Supply Chain (CSC) has invested in different sites of its R&D business, such as those in Great Valley, Pennsylvania, US, and Montpelier, Vermont, US, to expand its chain capacity and capabilities. This has included incorporating new technologies to connect with patients to achieve better compliance, and using digital capabilities to secure inventory and cold chain, and develop elabelling.

Data analytics are currently being used to better articulate demand management and operations.

"Sanofi CSC is implementing a tool to serve as a backbone across clinical and supply chain dimensions, and to be extended to chemistry, manufacturing and controls (CMC) as an end-to-end solution, helping to achieve the best clinical execution by balancing risk and cost while optimising manufacturing quantities," Basseras explains.

At the crossroads of clinical, preclinical and regulatory pathways, he believes, CSC is becoming a "control tower within R&D ops to help align demand and execute operations".

So, in a fast-changing landscape, what does the future hold?

"Gene therapy will be one new challenge to overcome through CSC, alone and through partnerships, because it requires treatment delivery at -80°C," explains Basseras. "Pharma companies will also have to continue embracing the digital patient journey to accelerate treatment development and delivery in areas of unmet patient need." ■

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Solving speed, agility and cost

Time is of the essence for clinical supply teams, and as a result so too is the need to secure agile clinical supply sources. Produced by **RxSolutions**, the RxStudy Card brings time and cost efficiency to traditionally difficult clinical trial supply management, making it easier than ever for trials subjects to use local pharmacies to acquire non-IMP drugs and supplies.

Speed, agility and funding are common topics among clinical supply teams. And while there are a number of ways to secure funding for a focused study, there is no way to buy more time. However, one can look for a more agile clinical supply source.

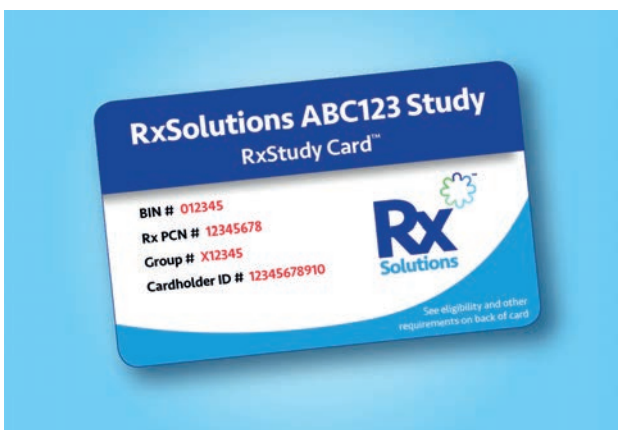
Until recently, clinical trial supply managers had only two options for controlling these conditions. One – keep all the logistics and supply management in-house, effectively becoming a distributor for the trial subjects, with all the headaches and regulatory hassles that ensue. Two – partner with a supplier or pharmacy to provide non-IMP medications and supplies to the trial subjects, but then leaves supply managers stuck with the administration and management required for reimbursements, insurance, risk and cost through the life of the study.

To put it simply, neither option is ideal. Both can be frustratingly time-consuming, inefficient, and more costly than necessary.

Supply management solution

The RxStudy Card is a first-of-its-kind, direct-to-patient clinical trial supply management solution that puts supply managers' three top concerns – speed, agility and cost – at the forefront. Developed by RxSolutions out of Raleigh, North Carolina, the RxStudy Card gives trial subjects the freedom to choose their own pharmacy from which to acquire their non-IMP drugs and supplies, thus eliminating the need to manage reimbursements and other headaches such as procurement, storage, shipping, temperature excursions and expiry date management.

As clinical trials are designed and subjects are recruited, the formularies of necessary non-IMP medications and supplies are designed as usual. But instead of sourcing those directly, those formularies are simply turned over to RxSolutions. It then customises a programme for each specific clinical trial, complete with study specific 'insurance-like' RxStudy Card that is provided to subjects with a prescription. Subjects receive the IMP trial drugs from the clinical trial supply team, of course, but all of their other drug therapies and supplies are acquired at pharmacies convenient to them with no out of pocket cost. There is no need to travel to the investigational site, which means they are more likely to adhere to the trial protocols, which makes it more likely for trials to be completed successfully and on time.



The RxSolutions card allows trial subjects to choose the pharmacy from which they can acquire their non-IMP drugs and supplies.

Clinical case studies

Wondering if it really works? Consider these two real-world case studies:

In Case Study A, an oncology trial required a standard of care medication that was extremely limited in production. Bulk sourcing was a significant roadblock that threatened to end the study before it began. RxSolutions worked directly with a speciality pharmacy to provide the required medication directly to patients via a central pharmacy, effectively green-lighting the study while also saving 34% – in this case, $58 million – over the traditional bulk supply method.

The problem in Case Study B was a bit different. In this case, the trial sponsor made a significant initial capital investment only to face slow enrolment. So slow, in fact, that the expiration date passed on $1 million worth of inventory before it could be used.

Hesitant to make that mistake again, the sponsor instead partnered with RxSolutions to provide trial subjects with an RxStudy Card, allowing them to obtain non-IMP medications directly from a retail pharmacy, where expiration date management is already systemised. No upfront investment was needed, and there was zero waste.

RxSolutions provide free consultation and analysis for anyone who thinks that the RxStudy Card may be the answer for their next clinical trial. With case studies and data to back up its claims, it's easy to see why the RxStudy Card is a true game-changer in the world of clinical trial supply logistics and management. ■

Further information
RxSolutions
www.getrxsolutions.com

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The changing face of clinical trials

Traditional trial strategies often bring challenges to patient recruitment and retention. Sponsors are eagerly embracing the value that hybrid and virtual trials offer, and are exploring how logistics and supply chain experts like **Marken** can work closely with them and with patients through these types of trials.

The growth of DTP (direct-to-patient) and DFP (direct-from-patient) supply chain services in recent years has been in response to the need for minimal disruption to the patient's lifestyle while increasing their willingness to participate in a clinical trial.

Patient behaviour, expectations and technology are driving the strong interest in virtual trials. Streamlining logistics, the strategic involvement of supply chain partners in the protocol design, and simplified patient-centric services, form the new model for planning a successful clinical trial. The main challenges associated with DTP and DFP services are often the lack of control over temperature-sensitive materials. Critical questions need to be addressed when considering adding a DTP protocol to a trial, such as how can all partners invovled effectively coordinate the different parties connected to the patient – site, logistics courier and home-care provider – or ensure patient data protection and privacy is maintained throughout the study across different suppliers?

Planning ahead

Sponsors need to understand the common regulatory challenges associated with home care, and DTP and DFP strategies. By exploring the set-up process for a successful trial and to avoid risk, critical points in operationalising home care and the last mile of the supply chain need to be addressed. Assess each protocol to verify which are most appropriate for DTP and DFP, and home healthcare, and review the types of procedures commonly conducted in home care. Patient data protection and privacy can become a potential pitfall. Marken continues to lead the industry in DTP and DFP supply chain solutions to meet the growing demand from the clinical trial industry.

Marken has demonstrated its ability to effectively manage drug product delivery to and biological sample pickup from patient homes, having adapted systems and processes to be compliant with patient privacy regulations. Pharmaceutical companies are becoming comfortable with the DTP service and it is Marken's belief that the majority of clinical studies will eventually be conducted with a DTP, DFP and home healthcare service feature.

As the clinical trial industry moves towards more personalised treatments, Marken is ensuring its services evolve for these more complex and specialised trials. DTP services are the fastest-growing part of the business. The company currently manages more than 1,600 DTP and DFP monthly deliveries in 51 countries.

Signed, sealed and delivered

Marken recently announced a new service that allows nurses to drop off clinical trial samples at UPS store locations across the US. Nurses are able to drop biological samples with various temperature ranges at local UPS stores that serve as a conduit for direct shipment to the selected central or speciality laboratory.

Close to home

Marken recently announced the development of its global home-based nursing network to supplement its existing services. The new home healthcare offerings includes intravenous infusion; blood draws; biologic sampling, such as pharyngeal and oral mucosal swabs; and the clinical assessment of vital signs and other mobile-based electronic data collection. The 24/7 Patient Communications Centre (PCC) and Marken's Viseo application enhance these services. The Viseo online interface allows patients and nurses to track their home deliveries of clinical trial materials and the pickup of their biological specimens via their mobile device or personal computer. Real-time driver traceability can translate into improved patient expectations and confidence with hybrid or virtual trials, and reduce the number of rescheduled deliveries and delays.

Marken has actively managed supply chain solutions for DTP trials since 2012, and has expanded its expertise to provide services throughout the world. It continues to anticipate the future needs of clients and patients alike. Marken recognises that the supply chain is a critical link in today's changing clinical trials environment. With its growing experience in DTP and DFP trials, coupled with a history of high touch, personalised service, the company will be able to reach populations in remote areas through home-based clinical trials with an unwavering commitment to patient safety and privacy. ■

Further information
Marken
www.marken.com

One strategy adjustment to accelerate clinical trials

Managing the complexities of a clinical supply chain is a critical part of drug development. *Clinical Trials Insight* talks to **Thermo Fisher Scientific**'s Franco Negron, president of pharma services commercial operations, and Leon Wyszkowski, president of the clinical trials division, about the cost and time advantages to sponsors of using a single-source supplier.

Is there data supporting the choice of a single-source supplier versus multiple suppliers?

Leon Wyszkowski: It stands to reason that a single-source supplier – one-stop shopping, if you will – would simplify supply chains while saving time and resources. Now, independent research conducted by the Tufts Center for the Study of Drug Development and recently published in *Clinical Therapeutics* appears to confirm that.

Tufts researchers compared dual-vendor (separate drug substance and drug product vendors) versus single-vendor contract development and manufacturing organisations (CDMOs) on cycle times and development costs. They concluded that sponsors enjoyed substantial financial benefits from using a single CDMO outsourcing model rather than multiple, fragmented vendors, even after accounting for somewhat higher sponsor fees. Benefits included millions of dollars in cost savings associated with shorter development times, enabling products to reach the market sooner.

What criteria should guide a sponsor in selecting a single-source supplier?

Franco Negron: Sponsors should seek a supplier capable of providing a fully integrated drug development and manufacturing solution – a partner for every step of the process, from substance to clinical trial to commercial product – with global reach.

This means a supplier with a proven ability to create or source ingredients, design the ideal formulation, scale to the next milestone, develop a clinical supply strategy, accelerate clinical research and deliver a successful commercial launch.

The ideal supplier should offer end-to-end, fully integrated solutions.

Regarding manufacturing, anyone can follow a recipe and churn out product. That's not good enough. A sponsor should look for a supplier capable of helping develop stable and scalable products with the right solubility profile, while reducing capital spent on raw materials or rework on formulation. The supplier should offer drug development services that include elements such as formulation and process development, because the aim is not merely manufacturing the sponsor's product, but manufacturing the best version of that sponsor's product or products.

> "Streamlined services will enable molecules to reach the clinic faster than ever before due to supply chain simplification."
>
> **– Leon Wyszkowski**

That requires additional capabilities. It means using a chemical API manufacturing process that uses the fastest, most stable route and a minimum number of steps. Fewer steps means decreased raw materials, which reduces cost when the sponsor scales up their drug substance.

It requires identifying and correcting solubility issues early in drug development, making certain that the formulation will scale as the molecule progresses from phase to phase.

With respect to biologics, it calls for assisting with cell line development and upstream/downstream process development to maximise yield and get the product to the clinic as quickly as possible.

LW: The supplier should be an expert at managing, optimising and streamlining the clinical supply chain from early strategy development through the enrolment, maintenance and closeout phases of a trial. This includes everything from study-planning and forecasting to logistics and shipping to clinics.

The supplier should also offer service options from which sponsors can choose, depending upon their needs. For example, clinical supply optimisation services to assist with clinical supply forecasting, planning and execution;

programme management to keep the molecule on its critical path; and total transportation management to help customers manage their transportation spend. This includes recommending the best transportation options to ensure that products arrives on time, in full and at the correct temperature, regardless of location.

What are the benefits of partnering with a single-source supplier?

LW: I spoke earlier about research indicating that use of a single-source supplier results in substantial cost savings to sponsors, as well as shorter drug development times.

For small and emerging companies, accelerating development can increase their companies' valuation and thus enabling them to continue to fund innovation.

For all sponsors, a single-source supplier mitigates risk. Minimal handoffs in the supply chain reduce communication gaps and the likelihood of problems, resulting in end-to-end visibility of supplies with improved process efficiency and overall metrics.

Another benefit is decreased administrative burden. A single supplier minimises the time and personnel required for a sponsor to manage the relationship and handle paperwork. While a reduced administrative burden is relevant to all sponsors, it's particularly important for small companies managing limited resources.

A relationship with one supplier also facilitates nimbleness, flexibility and problem-solving. Sponsor and supplier can identify solutions quickly when problems arise, ensuring that drug supplies reach the patients when they need them.

How is use of single-source suppliers likely to impact the industry?

FN: We're seeing the effects of contract development and manufacturing (CDMO) consolidation on the way in which pharma companies are outsourcing. I predict that we'll continue to see greater consolidation of outsourced services in the form of additional acquisitions, enabling the big players to rise to the top.

Pharma companies should use these developments to their advantage, rather than fragmenting their outsourcing across multiple small vendors that could potentially go out of business.

LW: Exactly. Streamlined services will enable molecules to reach the clinic faster than ever before due to supply chain simplification.

Many small companies reject the idea of building a secure supply chain early in development because they perceive it as too expensive and time-consuming. What they don't realise is that when a compound enters Phase 2b, company valuation will be higher if a sophisticated supply chain is in place. If a company is managing multiple suppliers and switching suppliers throughout the development process, it won't have a single source of documentation, project management or accountability. Management may want to consider these elements if their exit strategy involves selling the company.

When outsourcing, companies should choose a supplier that will ensure a secure supply chain where all clinical trial material reaches clinics on time.

Which sponsors benefit most from working with a single-source supplier?

LW: The full continuum of sponsors – from large pharma companies to emerging biotechs – stand to benefit from working with a single-source supplier, although they have different needs when they outsource services.

Large companies can choose between insourcing and outsourcing. When they opt to outsource, they should choose a supplier that will ensure the establishment of a secure supply chain and that every batch of clinical trial material reaches clinics on time. The focus must be on consistent and reliable delivery, because patients are waiting.

FN: It's also worth noting the difference in circumstances with respect to emerging biotechs. Unlike large pharma companies, most biotech companies don't have the luxury of deciding whether to insource or outsource, or the funding to invest in capital assets. In working with a small company, a single-source supplier acts as an extension of that customer's team.

For small companies, it's about giving their molecule the best chance at success – and doing that quickly. It's about maintaining the focus on the customer and enabling the customer's success.

What advice would you offer sponsors about working with single-source suppliers?

FN: Engage with the supplier in a strategic rather than a tactical way. In the past, the relationship between a sponsor and a supplier was largely tactical, but it has evolved over the years. That's a good thing.

By acknowledging the expertise that each brings to the table and working together, a sponsor and supplier can generate value for the sponsor and, ultimately, contribute to the improvement of human health. ■

Further information
Thermo Fisher Scientific
www.patheon.com
www.fisherclinicalservices.com

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Perfect harmony

The way clinical trials are conducted in the EU will experience a significant shift when Regulation (EU) no. 536/2014 (termed Clinical Trial Regulation) is implemented in 2019 and this has created a lot of uncertainty for member states. Louise Thomas discusses the key changes arising from this legislation and how clinical trials will be affected.

The objective of the new European regulation, applicable in all member states, is the harmonisation of the approval process for clinical trials and the introduction of a common evaluation for multinational trials. This is achieved through reducing bureaucracy during the authorisation procedures. The decision for 'regulation' rather than a 'directive' prevents regulatory autonomy at a national level in member states. However, this means that the rules are applicable throughout the EU.

The central aspects of the legislation include an authorisation dossier, a single portal for submitting authorisation applications, and a rapid evaluation procedure involving all the member states where the trial will be conducted as well as precise time frames.

The first application of the regulation commenced in September 2018; Directive 2001/20/EC remains valid for a maximum of three years after the application date of the regulation. There will be a transition period for the old and the new procedures, which means that both will be in parallel for a maximum of three years. An application for

approval may be submitted one year after its entry comes into force, in accordance with the old or the new legislation.

Decisions, decisions

The new regulation defines a clinical trial as having three criteria. The first of these is to investigate or confirm the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products. The second is to detect any side effects of one or more drugs. The third is to study the absorption, distribution, metabolism or excretion of one or more medicinal products, in order to establish their safety and/or efficacy.

A clinical trial is also clearly distinguished from a non-interventional study. If a study meets additional criteria, it is defined as a clinical trial. This criteria includes a candidate that is assigned in advance to a specific treatment strategy that does not correspond to the normal clinical practice of the member state concerned; if the decision to prescribe the experimental medicinal product is taken at the same time as the decision to include the subject in the clinical trial; or if patients are undergoing diagnostic or monitoring procedures that go beyond normal clinical practice. If a clinical study does not meet any of these conditions, it is considered a non-interventional study and the regulation does not apply.

by a member state that will act as rapporteur.

Clinical trials will also be categorised as being either traditional or low-level interventions. There is also a significant increase in transparency of the data generated, with a greater involvement of the public and patients. This includes the introduction of a patient into the research team and the publication of a final report in plain language.

The evaluation report produced must be divided into two sections, science and ethics, which can be presented at the same time or in separate phases. The final decision lies with the member state. In terms of the science part, this needs to include a statement of knowledge, clinical question, hypothesis to be tested, clinical relevance, goals, end points, safety measures as well as risks and benefits. The ethical aspect must include patient information, informed consent, a letter to the treating physician, details on how to enrol, insurance, suitability of research team and site as well as any refunds. The rules allow for free choice of the involvement of ethics committees during the evaluation process, as long as this falls within the established time limits.

Clinical clarity

In November of this year, the EMA released a new document summarising the changes to the Clinical Trials Regulation. The agency has now provided clearer guidance on the publication of withdrawn applications in cases where it will be resubmitted in the future. The new guidance notes state: "In light of the resubmission of the regulatory procedure, the agency will generally consider the postponement of the publication of the clinical data package for the withdrawn marketing application, with the understanding that the clinical data package will be published for the withdrawn product, once there is an outcome of the decision-making process for the resubmitted regulatory application."

Clarification was also made on the publication of studies when the trial is still ongoing.

"Exceptionally, in cases where the main period/phase of a clinical study is still ongoing at the time of publication, this specific study will not be subject to publication until the last subject completes the study. In such cases, the applicant/MAH will be asked to provide a statement for publication where they commit to submit the study once completed. The other clinical documents that were considered during the evaluation and formed part of the decision-making process remain subject to publication."

> "A key aspect of the new regulation is close cooperation between the member states, with a single submission of the application for experimentation in all states in which the trial will be conducted."

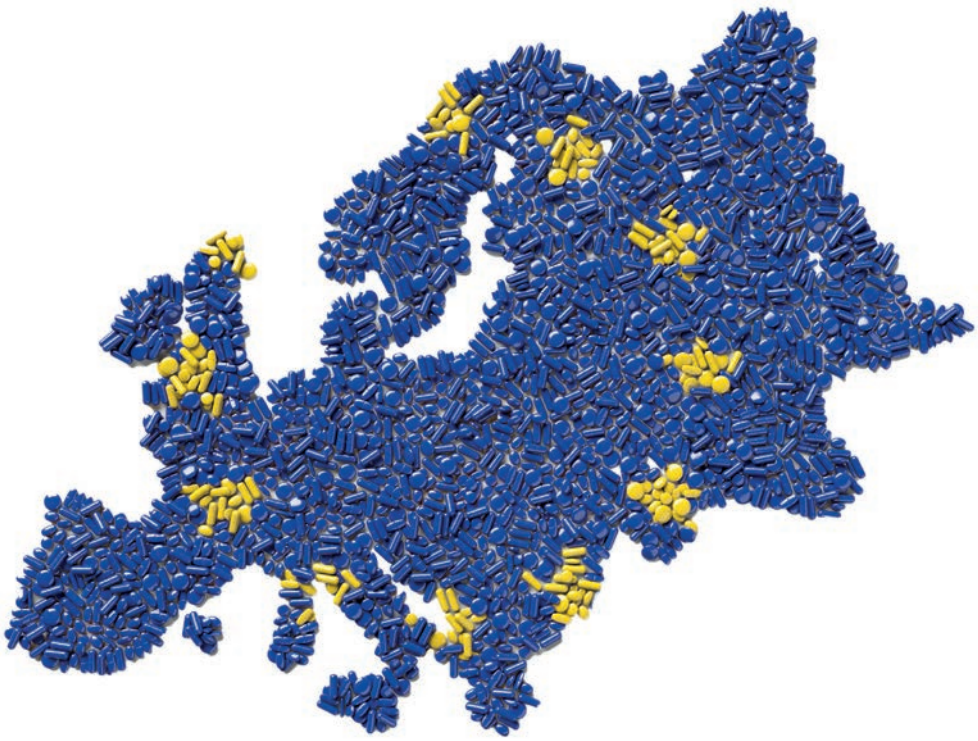
Close cooperation

A key aspect of the new regulation is close cooperation between the member states, with a single submission of the application for experimentation in all states in which the trial will be conducted. This also includes a joint assessment by all national authorities, guided

Steps for end-to-end publication of clinical reports

The revised guidance released by the EMA In November of this year included a more explicit explanation of the main steps of the end-to-end process for the publication of clinical reports:

Day 0: submission of the Redaction Proposal Document package by the applicant/MAH.
Day 1: receipt of the Redaction Proposal Document package by the EMA clinical data publication team.
Day 10: validation outcome is sent to applicant/MAH.
Day 47: redaction conclusion is sent to applicant/MAH.
Day 54: applicant/MAH provides written agreement to the redaction conclusion on CCI.
Day 61: upon request, Zapplicant/MAH provides updated anonymisation report and/or written responses on the recommendations/comments on the anonymisation report.
Day 74: submission of the Final Redacted Document package by the applicant/MAH.
Day 84: publication of the Final Redacted Document package.



> "There will be a single EU number for each clinical trial, an EU number for each medicine without marketing authorisation, information in an accessible format and an interface for users in all EU languages."

The update also included additional guidance on the potential need to submit an updated anonymisation report and/or written responses to the comments transmitted by the EMA on the anonymisation report before the submission of the Final Redacted Document package.

"During the consultation phase, in parallel with the assessment of CCI, EMA will also review the anonymisation report to check whether the applicant/MAH followed the anonymisation guidance and applied it consistently throughout the documents. EMA will transmit its comments (by Day 47), if any, to the applicant/MAH but does not formally adopt the anonymisation report.

"If required, the applicant/MAH will be asked to send a revised anonymisation report and/or written responses to the comments transmitted by EMA (by Day 61). The agency will review the documents and conclude on whether the comments have been addressed in a satisfactory manner. The outcome of the final review will be communicated to the applicant/MAH within seven calendar days from the date of receipt of the revised report and/or the response document.

"If required, the applicant/MAH will be asked to send a revised anonymisation report and/or written responses to the comments transmitted by EMA by Day 61."

The text was amended to address flagging the availability of a checklist to assist applicants/MAHs with the preparation of the Final Redacted Document package.

"In order to support applicants/MAHs with the preparation of the Final Redacted Document packages, a validation checklist is made available in annex 1.14. Please note that this checklist should be seen as an additional tool meant to improve the quality of the submitted packages and should not be included in the submitted document packages."

Streamlined standards

Compared with Directive 2001/20/EC, these standards have been simplified to allow for more efficient trial procedures. This includes an option for the experimenter to refrain from notifying the sponsor about adverse events if this is provided in the protocol. In addition, there is a direct disclosure of suspected negative side effects by the sponsor to the European EudraVigilance database and a more straightforward presentation of the sponsor's annual security report. Furthermore, the annual safety report is not presented for authorised medicinal products that are used within the limits of their authorised indication.

The regulation will also form the basis for the creation of a freely accessible EU clinical trial portal and database containing information on all ongoing trials in the EU. The portal aims to provide a hub for all communications on clinical trials in Europe. There will be a single EU number for each clinical trial, an EU number for each medicine without marketing authorisation, information in an accessible format and an interface for users in all EU languages. The database will be continuously updated and available to the public unless the information is considered to be confidential – personal data, for example.

The new regulation will pave the way for a rapid approval process and improved communication between sponsors, national authorities and ethics committees. Although the short processing deadlines and the complex assessment procedure require a high level of technical competence, the legislation should facilitate an increase in the amount and quality of clinical trials within the EU. ■

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Strategic acquisition

Covance's acquisition of scientific process outsourcing (SPO) company **Sciformix** strengthens its position in the later phases of drug and device development, particularly post-marketing pharmacovigilance and market access solutions. We speak to Manish Soman of Sciformix about what this acquisition means for both companies.

Covance recently acquired Sciformix – can you tell us why?

Manish Soman: Covance acquired Sciformix in the summer of 2018 to further enhance its post-marketing capabilities and continue to grow its leadership position in drug development solutions. Covance has been expanding its offerings in the late-phase/post-marketing space and seeking a greater global footprint. Over the last decade, Sciformix has proved to be best in class in both.

Additionally, with most of our employees in India and the Philippines, Sciformix extends Covance's ability to offer its clients a cost-optimised global delivery model. The two organisations are recognised for their commitment to scientific and therapeutic excellence, and quality services.

With Sciformix's deep domain knowledge in the post-approval safety and risk management space, it is a welcome and strategic addition to the Covance family.

Covance acquired Chiltern in 2017 and has a history of acquiring and integrating companies into its fold that broaden its portfolio and strengthen its ability to deliver best-in-class service capabilities. Together with Chiltern and Sciformix, Covance will leverage their greatest strengths and support its work in transforming drug development through innovation and greater efficiency.

Another benefit our clients will reap is enhanced innovation and operational transformation via technology and automation. For example, Sciformix has introduced some pretty neat solutions for safety in risk management, from basic and robotic automation to the fast-paced cognitive and AI technology space.

Covance is known as a CRO – is this changing the market position of the company?

Covance has always been known as a best-in-class clinical trials partner. Of the top 50 products that were introduced in the US in 2017, 49 of them were associated with Covance. The expectation of pharma is to have strategic partners who can provide full service offerings, including data services and post-marketing expertise. Clients now demand a full service offering that goes beyond early development and clinical services to post-marketing safety, regulatory and data services.

Covance has been working with its clients on many post-marketing initiatives for some time. It is a natural progression to continue providing client's insight after clinical trials.

For example, as our partners seek to launch and sustain their products in the market place, our 50-plus market access consultants are helping them develop strategies that derive and communicate stronger product value. We support some of the largest patient support and reimbursement programmes, as well as phase-IV trials and studies. With Sciformix's comprehensive post-marketing pharmacovigilance (PV) capabilities, Covance can now extend its PV support beyond the clinical trial phase.

> "Consumers are becoming increasingly more engaged in their own healthcare decision-making, so healthcare stakeholders must evolve their strategies to address the needs of patients as consumers."

Can you tell us more about how patients and consumers are playing a more active role in the late and post-approval phases?

As consumers move from recipients to participants across the entire drug life cycle, the industry needs to align strategies and business models that have patient centricity at their core. Consumers are becoming increasingly more engaged in their own healthcare decision-making, so healthcare stakeholders must evolve their strategies to address the needs of patients as consumers. Our clients are seeking solutions, tools, and information that will help them focus on costs, quality, efficiencies and convenience.

They are also looking to establish and extend the value of their products and provide patients with better support and access to drugs, all while ensuring proactive and efficient patient safety. Our clients need to support and educate doctors and HCPs about their products so they are equipped to serve patients in the best possible way.

Covance now has a broader portfolio of late-phase/post-marketing solutions to fill this need, such as real-world evidence and market access; safety and risk management; patient support and field service; phase-IV studies and trials; and regulatory affairs services. ■

Further information
Sciformix – a Covance Company
www.sciformix.com

Through the keyhole

A number of strategies are being developed to help the UK compete in the global research market post-Brexit, including the creation of 'high-throughput centres' to accelerate phase-II and III trials. **Jonathan Sheffield**, chief executive of the NIHR Clinical Research Network, speaks to Louise Thomas about the potential of these centres to deliver efficient patient-focused clinical trials, thus increasing the speed of getting drugs to market.

With 'Brexit Day' looming, the UK is in need of quick and effective solutions to remain an attractive location for clinical trials. Currently, it is responsible for 3% of the global drugs market. This will be put at risk by exiting the EU, which is likely to see the UK no longer part of EU clinical trial regulations. However, this depends on the final shape of any Brexit deal agreed. One promising solution is the creation of 'high-throughput centres,' which could help to cut regulatory approval times and speed up the delivery of trials nationwide.

This was put forward in a white paper by clinical trials accrediting company IAOCR and Jonathan Sheffield, chief executive of the UK Government-funded NIHR Clinical Research Network. Sheffield is a trained doctor, and worked as a histopathologist at Yeovil District Hospital before becoming a medical director. In 2009, he was awarded an

OBE for services to the NHS and, in 2011, he was elected an honorary fellow of the Royal College of Physicians' Faculty of Pharmaceutical Medicine for his contribution in the area of clinical research delivery. As a passionate advocate for clinical research, Sheffield's ambition is for participation in a study to be a standard treatment option for all patients within the NHS.

The proposal of high-throughput centres has come in response to the Life Sciences Industrial Strategy (LSIS) published in August 2017, which pledged to increase the number of clinical trials conducted in the UK over the next five years by 50%. Sheffield is confident this target can be achieved. This is particularly timely, not only in light of Brexit, but also due to recent clinical trial participation trends in the UK.

"What we've seen over the last seven to eight years is a massive increase in the amount of trials and patients that we are recruiting for them," says Sheffield. "The purpose behind these centres is to give increased capacity to the NHS to deliver these trials and make sure they are protected from clinical pressures."

Stepping up to the plate

Sheffield is acutely aware of the existing challenges of conducting trials within clinical settings for patients and staff.

"We often have to run trials in busy clinical environments and that puts pressure on the time that the patient has while they are involved in the trial, but it also puts pressure on staff," he explains.

However, he remains confident that these centres can meet the needs of clinical trials, without adding to the high burden already on NHS staff.

Sheffield is keen to ensure the smooth running of trials for patients as well as staff and has no doubt that high-throughput centres can achieve this aim.

"We believe that these centres will create the right ambience and facilities to make the conduct of a trial efficient and effective, while also giving an excellent experience for patients," he says.

His enthusiasm for the UK as a valuable location for conducting trials is clear.

"The UK is one of the best places, if not the best place, to conduct clinical trials," he says. "We have a diverse population who are engaged in research and want to be involved."

In light of these benefits, he is confident that the UK can not only maintain its current high rate of trial delivery but even increase this over the next few years.

"We're 3% of the global drugs market, but we believe that we can deliver 5% of the global market's trials," he says.

The increase in trials not only stands to benefit industry but also the NHS as a whole.

"We talk a lot about continuous quality improvement in healthcare but the ability to dramatically transform people's lives comes from research," Sheffield says. "That's an integral part of the NHS."

Although passionate about the potential of high-throughput centres to benefit patients across the UK, Sheffield remains mindful of the needs of the global clinical trials market.

"The biggest problem for the international clinical research industry is getting these studies done quickly, efficiently and effectively," he says.

Barriers to this process can include regulation, contracting and set-up. However, Sheffield has no doubt that these centres can overcome these challenges.

"What these centres will offer will be rapid regulatory approval and implementation," he says." This will allow us to have a very slick, lean process."

Sheffield knows that time is money for the industry but his confidence about the capabilities of these centres cannot be assuaged.

"Every day is a day off the patent licence for that drug but also a day of lost revenue if the drug's not licensed," he says. "We believe that we can help the global life sciences industry to deliver their studies quickly."

Despite his optimism, Sheffield knows that these centres must prove themselves before widespread roll out, and plans have already been put in place. A site is in development and due to go online in January. This will be followed by a pilot of approximately three to four additional sites to ensure they are able to deliver the capacity that industry requires.

The barriers surrounding implementation are also top of mind for Sheffield. One of these includes the challenge of getting time-strapped NHS organisations to come on board.

> "We need a consistency in the way that we operate. It has be recognisable to industry that the processes are the same across those institutions."

However, Sheffield is confident that NHS organisations will soon be keen to become involved.

"It should be seen as a badge of honour that you get one of these centres for delivery," he says.

Although enthusiastic about the potential of high-throughput centres, Sheffield is aware of the need for high standards to ensure efficient trial delivery. He plans to create a competition where the organisations explain why they would be the most suitable location.

"I think competition is always a healthy way to encourage the best," he says.

Running like clockwork

Once the centres are up and running, it is of course important to maintain a high quality of trial delivery. Sheffield is clear on what is needed to achieve this.

"We need a consistency in the way that we operate," he says." It has be recognisable to industry that the processes are the same across those institutions."

This isn't just an aspiration; Sheffield has spent considerable time and thought on how to achieve uniformity. He envisions something similar to a franchise model, where the processes remain the same in each centre to avoid variability in standards across sites. ››

The 2017 Life Sciences Industrial Strategy pledged to increase the number of clinical trials in the UK over the next five years by 50%.

Acutely aware of the need for speed, Sheffield knows that this consistency cannot come with delays.

"It will be really clear that there's rapid rollout from one centre to the other centres that you require to recruit patients to," he explains.

This will involve a standard sign-off so that if a trial has already received approval at one site, this will be sufficient for all other locations involved.

To achieve high standards across all trial sites, Sheffield is also keen to take advantage of technological capabilities. He plans to have IT systems in place that provide visibility of what is happening in each location involved in a trial.

"We want to track the performance of these centres in real time to make sure that they're delivering what they said they would do," he says.

A bright future

In addition to maintaining quality of trial delivery, Sheffield wants high-throughput centres to be forward-thinking in terms of study design, which will include testing new research methodologies. Involving patients is a key part of this strategy.

"At the moment we tend to treat patients as being the subjects of research but we want them to co-produce research with us," he explains.

> "We believe that these centres will create the right ambience and facilities to make the conduct of a trial efficient and effective, while also giving an excellent experience for patients."

Being patient-centric is also imperative to ensure that there is a steady stream of willing participants for trials. This is especially important in trials drawing from a small patient population.

"If we're only recruiting one patient per five million of the population for a rare disease, we can't expect them to travel vast distances," he explains.

Sheffield has high hopes of being able to target all types of patients across the UK effectively.

"These centres would allow us to deliver multiple studies at one site and that can be mirrored in multiple sites around the country so there is a constant ease of access for patients," he says." That for me would be the perfect vision for the future."

High levels of patient involvement not only benefits the trials themselves but also the level of care offered by the centres conducting the studies. This spans much further than the immediate participants in the study.

"It isn't just an effect on the patients involved; even those who aren't in a clinical trial have better outcomes than patients in institutions without many clinical trial opportunities," Sheffield explains.

Clearly communicating these benefits is key to selling high-throughput centres to NHS organisations. Getting those organisations to buy-in is unlikely to be easy, but Sheffield remains optimistic about the future of clinical trials in the UK.

"I genuinely believe that we will be able to increase the number of trials because the NHS is such a good environment to do them in," he says. ■

Straight to the source

Choosing between full-service and functional-service outsourcing models isn't a new debate in the pharmaceutical and biotech industries, but balancing the need for high-quality results, cost-effectiveness and time savings remains a challenge. Patrick Kingsland investigates the features of both models and looks at how to navigate complex outsourcing decisions.

In the past, pharmaceutical and biotechnology companies were known for discovering and developing their own drugs and devices – designing, testing and eventually bringing products to the market for mass consumption. But in more recent decades these companies have increasingly turned to a new group of players to perform services on their behalf: contract research organisations (CROs).

By promising to make operations faster and leaner while simultaneously offering a higher success rate, CROs that specialise in services as diverse as medical writing, data analysis and managing regulatory affairs have become an essential part of the clinical trials landscape.

A wider reach

With larger pharmaceutical companies continuing to downsize and smaller firms lacking clinical experience, it is a role that continues to expand. According to a 2018 report by Grand View Research, the global CRO market is expected to reach $51.3 billion by 2024, with a CAGR of more than 6% from 2015 to 2022. ››

The report cites North America as the largest CRO market due to the number of trials undertaken and outsourced, with considerable support from the US Government for different R&D activities. Asia-Pacific is cited as the fastest-growing region thanks to its diverse population, and ability to recruit and retain patients for trials with relative ease.

"The key reasons for the rapid growth include increasing investment in R&D programmes, preference to outsourcing activities due to time and cost-efficiency, and patent expiration," says the report. "The contract research outsourcing collaborations offer cutting-edge services, and thus government organisations prefer assigning projects to the CROs."

As the CRO industry grows, it is undergoing a number of important structural changes. First, it is having to cater to new clinical services in the fields of technology, patient services and regulatory affairs, where expertise is particularly important to help reduce costs and guarantee approvals.

Second, in recent years the largest CRO organisations have embarked on projects of aggressive consolidation. The industry's top ten players now account for around 60% of the entire market and are gradually squeezing out smaller companies by offering as large a range of services as possible.

Close to home

CROs have also been trying to get much closer to patient data in an attempt to improve their ability to recruit and retain people for studies – a common thorn in the side of the clinical trials industry. In January, for example, multinational company Parexel announced a new partnership with Optum, an information and technology-enabled health services business. The alliance will see the CRO gain access to data on roughly 35 million patients.

"Leading CROs are aggressively seeking game-changing strategies to enhance their relevance, secure competitive advantage and measurably impact sponsor-company development performance," says Getz.

As well as forcing CROs to evolve, increasing regulatory pressure and commercial competition are driving sponsors to evaluate which outsourcing models will help push their clinical trials forward. Over the past few years two models have emerged at the forefront: full-service outsourcing and the functional service provider (FSP) model.

Going all in

As its name suggests, the former involves sponsors outsourcing entire clinical trials or programmes to CROs that are considered capable of providing all the functional services required.

> "According to a 2018 report by Grand View Research, the global CRO market is expected to reach $51.3 billion by 2024."

Third, large CROs are now pursuing bold new strategies designed to enhance their competitiveness. According to an article by Ken Getz from the Tufts Center for the Study of Drug Development (Tufts CSDD), a number of major CROs have taken the step of physically acquiring investigative sites and site networks. This can be seen in PPD's 2015 acquisition of Clinical Research Advantage and 2016 purchase of Synexus, the world's largest global site-management organisation.

It is a classic tried-and-tested approach that enables vendors to leverage their own systems in a cost-efficient fashion.

"Full-service outsourcing provides the benefits of access to scale and less complex management versus the use of multiple providers that have to interface with each other," say Lina Cohen and Allie Young, researchers at Gartner and authors of the book *Multisourcing*.

But the approach can encounter problems. In many cases, sponsors report feeling stuck with a single service provider that may not be performing adequately in certain areas. Duplication of roles is often reported, with both parties engaging in oversight and strategic decision-making – and neither quite sure who is really in charge.

Over the years, these limitations have led to a surge in interest in FSP-based outsourcing – an 'a la carte' model in which vendors provide specific functions of a clinical trial such as monitoring, site management and bio-statistics. The contract terms of this model are usually focused on the service being delivered rather than the time and effort required.

Fit for purpose

The FSP model is often considered a more flexible approach to outsourcing. Instead of using one company to perform all services, sponsors can instead pick the most suitable service provider for each individual area.

"When working under a FSP model, a sponsor company can pick and choose among the best-in-class service providers to find the expertise needed for their therapeutic area," says Lisa Henry, senior manager of clinical research at the medical device company Cordis, for clinicaltrialsarena.com.

The model also allows sponsors to retain wider control over product delivery – something that is not possible when an entire clinical study is outsourced. This helps to avoid the pitfalls associated with full-service arrangements, when attempts at oversight end up producing wasteful levels of duplication.

But FSP models are certainly not perfect. They are not considered as mature as full-service arrangements and therefore lack the same level of understanding within the industry. Having multiple vendors delivering different services can also be difficult to manage and potentially result in an increase in costs.

"Each provider will need to incur costs associated with familiarising themselves with the project scope, the protocol and attendance at start-up meeting," according to *Applied Clinical Trials*, a peer-reviewed journal that covers clinical trials management.

"It is important to take into account the increase in both project management hours and costs resulting from the effort required to oversee and manage functional outsourcing providers."

Despite sponsor organisations exploring various outsourcing formats, around 40% are yet to find the clinical development outsourcing model that works best for them, according to a recent study by pharmaceutical markets-research company ISR Reports.

"The problem with that number is that it leads to churn and uncertainty for both the sponsor organisations and the service providers," says Andrew Schafer, president of ISR Reports.

The CRO industry's top ten players now account for around 60% of the entire market.

Room for improvement

Whatever model is chosen, the operating performance of drug development has not substantially improved across the industry, according to Tufts CSDD. Drug development failure rates are higher now than they were in the 1990s, while development cycles are longer and patient recruitment and retention rates are lower. Drug development costs, meanwhile, are escalating.

A recent Tufts CSDD report argues that the majority of studies involving CROs and sponsors are not implemented as intended, with executives from both parties pointing to a lack of trust and poor communication as major obstacles to successful collaborations.

> "Drug development failure rates are higher now than they were in the 1990s... drug development costs, meanwhile, are escalating."

The CSDD report goes on to claim that pharmaceutical companies regularly treat their CROs as vendors rather than invested partners, with over 80% of CRO respondents saying that vendors rarely, if ever, ask for or implement their suggestions.

Outsourcing arrangements are also often decided on an ad hoc basis, changing their form from study to study with little or no standardisation and lacking discipline, with sponsor organisations opting for a number of different, sometimes paradoxical arrangements that ultimately end up creating uncertainty.

"Sponsor companies use a variety of conflicting outsourcing models to support their studies, mixing and matching the use of internal staff with niche and full-service providers under various relationship arrangements simultaneously," says Getz in a 2016 article for *Clinical Trials Yearbook*.

According to Getz, many of these problems are due to the large, fragmented nature of big sponsor companies, the clinical teams of which are often unaware of which outsourcing arrangement is being used.

Teaming up

The issues can get worse when new partners arrive, with clinical teams often averse to "handing over existing projects to new partners" and, worse still, when companies experience mergers and acquisitions. Problems are also triggered by turnover of senior staff overseeing the outsourcing arrangements.

"Partnerships are prone to fall apart when new executives, who might have different ideas about sourcing models, take charge," says Getz.

Some pharmaceutical companies have brought certain functions back in-house, but most will continue to rely on outsourcing. Analysts say the solution is to find the right sponsor-CRO match and build a relationship based on trust, strong communication, and shared goals and culture.

Shifting gears

"Sponsor companies must fundamentally change their outsourcing execution to capture a higher proportion of expected collaborative value," says Getz. "Introspective assessment of current practices will play an important part in identifying opportunities to drive more consistent outsourcing execution. In-depth, open discussions with CRO partners will be equally revealing."

What outsourcing models are chosen in the future will depend on how the industry changes. Clinical development may be a closely regulated industry, but the companies, technologies and science involved are always evolving.

"There is a saying in clinical development that 'every study is different'," says Schafer. "Each trial is unique in some way. Sponsor organisations and service providers will continually change the way they conduct clinical trials, and that includes the models used in order to provide the best service possible at a reasonable cost." ■

Africa: an advantageous landscape for conducting clinical trials

Africa has immense potential as an emerging market, and pharmaceutical and biotech companies have many avenues to leverage from **Barc Lab**'s African footprint for running clinical trials.

Accounting for nearly 17% of the global population, and representing a diverse population of potential patients, the African continent offers many of the best conditions for conducting clinical trials. Importantly, a number of diseases – particularly those defined as neglected and tropical – are endemic to the developing world, which includes Africa. Despite all these advantages, Africa contributes to less than 3% of the number of clinical trials. The lack of infrastructure, cultural barriers and dedicated staff, and misunderstanding of requirements to work in the region, are simultaneously causing a burden to conducting clinical trials within Africa. However, Barc Lab believes that Africa offers an enormous opportunity for pharmaceutical and biotech companies searching for low-cost study sites, low risk of litigation and a diverse patient population. The latter makes Africa an ideal location for research, as the diseases of affluence and poverty are prevalent. Moreover, the majority of patients to be potentially enrolled in clinical trials have not received any previous treatment for their disease – either because it is not available or they cannot afford it – facilitating patient recruitment to a great extent.

Joined-up engagement

Barc Lab, part of Cerba Healthcare Group, has been focusing on central lab activities for the past 35 years. It has established a portfolio of customers, based in Europe and the US, who need to expand to the Africa region in order to easily enroll participants into both interventional and non-interventional studies. Barc Lab can draw on the support of the Cerba HealthCare and Lancet networks, who have joined

Barc Lab's footprint in Africa, comprising of the Lancet Laboratory (light blue) and the Cerba HealthCare (dark blue) network of labs, across a total of 23 countries throughout Africa.

forces to become the medical biological and diagnostic leaders in Africa. With over 11,000 collaborators who share the same goal for providing patients, physicians, pharmaceutical and biotech companies with the best healthcare service, CerbaLancet ensures that patients, irrespective of their geographical location, benefit from proximity, quality and innovative biology. This new joint venture follows a successful collaboration between the two diagnostic leaders and creates a network with coverage in over 23 African countries. The establishment of this joint venture, and the increased resources within the group in Africa, make this the ideal opportunity for Barc Lab to expand its activity across the African continent and become the global leader in central laboratory services in Africa.

Identifiable data

Barc Lab, together with the Cerba HealthCare group and the Lancet Laboratories network, is working extensively to use digital technology to help identifying patient population across Africa. It can give its clients access to reams of patient data, either through diagnostics or biological profile. This approach has the potential to expand the number of clinical trials throughout Africa conducted in any setting, including low-resource settings.

In fact, Africa can be considered a 'greenfield' site, allowing companies to exploit and introduce innovative approaches, and to use digital technologies to pinpoint where patients are based by searching through Barc Lab's database. With artificial intelligence (AI) maturing, Barc Lab is also engaging and implementing AI to optimise clinical trials. The company aims to gain insight into the data its gathers throughout clinical trials, including Africa. Combining data from electronic records on a global scale, Barc Lab is able to compare patient populations all over the world, and to help target the required geographic area with the eligible patient population for a particular indication. These AI-driven insights are data-intensive, and can increase the efficiency, and reduce the costs of clinical trials through improved protocol design and targeted patient enrolment.

As promising as this is, with regard to the concept of evidence-based medicine, additional clinical trials are needed in the Africa region to understand how treatments will affect African populations. Those results can be used to inform practice and healthcare guidelines. To overcome the lack of evidence from the African region, Barc Lab will work closely together with the Cerba HealthCare and Lancet networks to compile and deliver this information.

Move forward

With the expansion into Africa, Barc Lab will work with the local and regional stakeholders to mitigate risks and develop a comprehensive solution to run clinical trials for the pharmaceutical industry, CROs and NGOs. Barc Lab in Africa will be the ideal partner to provide the service and expertise to routinely conduct medical clinical testing under recognised US accreditation, thus ensuring that the tests offered are also performed daily for diagnostic purposes, patients' stratification, staging, therapeutic indication and follow-up.

Up until today, the focus on clinical research has primarily been on infectious diseases, particularly HIV/AIDS, TB and malaria, as large numbers of the country's population are greatly affected by these diseases. Nevertheless, cooperative clinical trial groups, sponsored by the National Cancer Institute, have already begun working in the Africa region, showing a large interest to also bring cancer therapies to Africa.

> "Africa can be considered a 'greenfield' site, allowing companies to exploit and introduce innovative approaches and use digital technologies."

As challenging as it may seem, Africa presents a unique profile that interests many pharmaceutical and biotech companies. Changing requirements – such as patient diversity and the need for greater subject numbers in clinical trials, in parallel with improved clinical research environments in African countries – are resulting in a notable growth in clinical research in the region. ■

Success story: Barc Lab South Africa

Barc Lab has established a portfolio of customers, based in Europe and the US, who need to expand to the Africa region to be able to easily enroll participants into large phase II or III studies. A joint venture between Lancet Laboratories and Barc Lab was founded in 1999, namely, Barc Lab South Africa. This has been a fruitful relationship and has established the groundwork for working in Africa. Barc Lab South Africa has experience with a broad client base who work, or would like to further their work, in Africa. According to many investigators, South Africa provides a better environment for clinical trials than many other African nations, and because of this it can serve as a model for clinical research in Africa and to help improve preventive care.

Partnering with Lancet Laboratories, Barc Lab has been able to set up and manage clinical trials in Africa for two decades. With a local team based in Johannesburg, Barc Lab South Africa has conducted multiple trials in a wide range of different therapeutic areas. Working closely together with the US National Institutes of Health (NIH), NGOs, CROs and pharmaceutical companies, Barc Lab has localised expertise which allows it to expand and execute trials in the entire Africa region, taking Barc Lab South Africa as an example. This expansion can be seen in the rest of Africa, as the laboratory infrastructure improves and acts as a catalyst for conducting clinical trials in the entire Africa region.

Further information
Barc Lab
www.barclab.com

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Dementia in the DNA

Alzheimer's disease is the most common cause of dementia, which currently affects over 46.8 million people across the world today. The ApoE4 varient of apoliprotein E (ApoE) is recognised at one of the most prominent genetic risk factors for dementia due to its implication with Alzheimer's-contributing factors, and is now screened for by the medical industry. **Randox Laboratories** has produced its Biochip Arrow Technology (BAT) platform to allow the direct identification of ApoE4 through simultaneous chemiluminescent sandwich immunoassays, which can also be performed by the company's Evidence series of biochip analysers.

In the context of an ageing population, the prevalence of neurodegenerative diseases is increasing worldwide; the estimated 46.8 million people worldwide living with dementia in 2015 will rise to 131.5 million by 2050. Alzheimer's disease is the most common cause of dementia, resulting in a gradual decline in cognitive function in sufferers. Current treatment options are limited to the alleviation of symptoms or the introduction of lifestyle or dietary adjustments aimed at slowing down disease progression, with no cure available.

In an effort to develop a deeper understanding of the disease, over a decade of research has established the physical basis for beta-amyloid-rich plaques, toxic accumulation of the tau protein in neurofibrillary tangles or the inflammatory components of Alzheimer's disease. Impaired clearance of lipid deposits in the brain tissue involving apoliprotein E (ApoE) is implicated in each of these phenomena, and accordingly, the ApoE4 variant of this gene is recognised as one of the most powerful genetic risk factors for dementia and other neurodegenerative diseases.

ApoE4 carrier status

As we enter an era of personalised medicine, screening for the ApoE4 variant is a consideration to allow those who choose this option to employ lifestyle adjustments, health monitoring, available countermeasures or to otherwise plan their lives accordingly.

Further, within the clinical trial industry, ApoE4 status is recommended for screening of subjects when investigating new therapeutics so that specific at-risk ApoE4 carrier populations can be identified. Patient advocate and peer support groups are emerging for those identified with ApoE4 carrier status to assist with the implications of learning one's status in addition to promoting the search for better outcomes for those living with Alzheimer's.

Emerging therapeutic strategies, including targeting the facets of Alzheimer's disease pathology in large scale clinical trials, have met with difficulties that include a lack of efficacy of promising preclinical drug candidates. Opinions differ as to the cause of these failures; either trials are being conducted on patients whose disease is too well established to benefit from the study drug, too narrow a focus on one aspect of the disease or perhaps the need for identification of the appropriate patients that would benefit. Taken together, a test for identification of ApoE4 carrier status that is rapid, cost-effective and easily implementable is highly desirable.

New methods for rapid identification

Presently, Molecular approaches are employed to determine a patient's ApoE genotype, using PCR of genomic DNA samples obtained from the subject. This process requires informed consent for sample collection, DNA extraction and analysis of genetic information, and specialised equipment not readily available or practicable in a routine clinical laboratory setting.

The Randox Biochip Array Technology (BAT) platform offers a potential solution through immunoassay plexing that allows direct identification of ApoE4 carrier status from a plasma sample. The ApoE4 Biochip identifies susceptible individuals through simultaneous chemiluminescent sandwich immunoassays for measurement of ApoE4 and total ApoE. This assay can be implemented through the highly versatile Evidence series of biochip analysers, from small laboratory to high throughput systems. Using the Evidence Investigator, the time from sample acquisition to result may be as little as three hours. Using the fully automated Evidence Evolution platform, a throughput of one sample per minute can be achieved along with the elimination of the sample handling requirements associated with PCR-based methods. Validation of the biochip-based ApoE4 genotyping assay has demonstrated complete concordance with PCR-based reference methods.

In conjunction with other emerging biomarkers, the ApoE4 array promises to be of major benefit for future diagnosis, risk monitoring and therapeutic targeting of Alzheimer's disease. With approximately 2,000 registered trials in Alzheimer's disease on ClincalTrials.gov – featuring monitoring and therapeutic intervention strategies – a rapid, efficient means of ApoE4 carrier status is not only essential, but is now available. ■

Further information
Randox Laboratories
www.randox.com

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Covance is one of the world's most comprehensive drug development companies, dedicated to advancing healthcare and solutions for its clients. It offers a range of solutions for the current issue of real-world evidence (RWE) generation, and other ways in which it helps its clients to optimise the clinical and commercial value of their brands.

Stakeholders often require evidence generated from real-world settings to make decisions regarding treatment, coverage and reimbursement. This is most evident in the recent passage of the 21st Century Cures Act, which requires the Food and Drug Administration (FDA) to develop guidance for the use of real-world evidence (RWE) in regulatory decisions on new indications and post-approval requirements for existing medical products.

Real-world evidence landscape

RWE is derived from the aggregation and analysis of real-world data (RWD). According to FDA authors of a recent *New England Journal of Medicine* article, RWD is collected from sources outside traditional clinical trials, through observational studies such as databases (electronic medical records and administrative claims, for example), chart reviews, product and disease registries, and prospective studies with or without interventions (visits, procedures, tests and so on). RWD can also be collected from pragmatic trials with a post-randomisation standard of care.

Improved technologies and the availability of platforms for patient identification, access and data capture open the door to innovative and efficient study designs to collect RWD virtually. Through consultation and collaboration, Covance experts determine the best study design to meet its clients' RWE needs. It seeks to challenge the traditional site-based paradigm by integrating virtual components into otherwise traditional study designs. As part of LabCorp, Covance can reduce the burden on investigators by collecting samples at LabCorp patient service centres when routine or esoteric laboratory tests are required.

Assessing the market

No matter where a product is in its life cycle, Covance works with its clients to maximise their product's commercial value. Part of this includes collecting and analysisng RWD and producing RWE for its clients. Covance Market Access works with clients to develop a complete market access strategy beginning as early as phase I. Covance can assess a client's market landscape, conduct research and communicate findings to help demonstrate value, augment clients' teams to help communicate their message, and support clients' patients, customers and overall access strategy. It offers solutions in five broad categories: access and strategy, evidence generation, value communication, patient support, and field services.

Real-world evidence (RWE) is derived from the collection and analysis of real-world data (RWD).

The goal of its outcomes research strategies is to ensure that its clients are on track to develop evidence to demonstrate the comparative value of their products and to meet the needs of patients, payers, providers and other stakeholders at launch.

Covance Market Access experts work with clients to develop evidence to support their value proposition. Companies need to demonstrate more than just clinical efficacy and safety to secure reimbursement in today's marketplace, and those looking to do so should turn to the experts at Covance Market Access to help generate the evidence needed to optimise value.

An ever-changing array of economic drivers, decision-makers, reimbursement models and regulations may impact the commercial value of companies' products in today's marketplace. The earlier a company begins developing its strategy, the greater the potential reward, and the more Covance can do to help its clients achieve their goals.

It's never too early for a company to start paying serious attention to this area, and to begin customising an optimal study design for its RWE needs. ■

Further information
Covance
www.covance.com

Compare and contrast

Choosing comparators is often an onerous process that involves navigating a lot of different models. A key decision is choosing between global and local sourcing. David Callaghan discusses the advantages and risks of different options, and how to determine the right partner for a trial.

One of the most difficult stages in the development of new treatments is choosing the right comparators to use in clinical trials. There are many factors to take into account before making a decision and the process involves negotiating a range of challenges.

The decision throws up a number of questions, including whether to source locally or internationally, and whether to source from one place or multiple locations. There are also commercial pressures like resistance from the manufacturers of the existing drugs, who are unwilling to cooperate with clinical trials for a rival product that may take its place in the market.

Comparators offer many advantages over the traditional placebo approaches, not least of which is the opportunity to offer a significant improvement on existing medicines.

Being clear about terminology is key, which was emphasised by Niklas Mattsson, head of comparator sourcing for pharmaceutical giant Merck & Co (MSD), in a previous interview with *World Pharmaceutical Frontiers*.

"The industry is talking a lot about comparators, but what they really mean is head-to-head comparisons," he explained. "You're comparing the new drugs with the standard of care in the market, and you're trying to prove you're either the same or better."

Comparators are available across all different types of drugs. "If you get approval for them, then there are all sorts of ones you can use; rescue medications or painkillers for headaches," said Mattsson. "You'd call them comparators, but the phrase really encompasses a lot of things – it's a head-to-head comparison of a blinded programme."

This doesn't necessarily involve comparisons between companies. "There are Merck drugs that we are using as comparators, too," said Mattsson. "But it is usually a one-off purchase, mostly through a vendor because they usually have contact with the manufacturers and it is the most practical approach."

Work in progress

Although discussions about comparators may seem to be a recent phenomenon, the World Health Organisation (WHO) recognised their complexities as long ago as 2002. At the time, it produced guidance, which has since been updated several times.

In the latest version, produced three years ago, WHO highlighted the ongoing challenges in the area.

"Large numbers of multisource (generic) medicines are being produced by many different companies and in different countries; this may result in different products," the guidance said. "On a global level there is thus a need to address not only the quality, safety and efficacy of multisource products that are exported and imported, but also their possible interchangeability."

The changing and challenging nature of the market has also been acknowledged by the US-based Tufts Centre for the Study of Drug Development.

"The lack of fully robust supply chain management practices, growing emphasis on expensive biologics, changing regulatory requirements and growth of counterfeit medicines are forcing drug sponsors to rethink and redesign their comparator drug supply chains to support drug development that, increasingly, crosses international borders," said Tufts Centre director Kenneth Kaitin in its 2014 report.

As a result, trial sponsors are increasingly investing in their comparator supply chains, including their own in-house capacities, in an attempt to be first to the market.

Solutions for sources

Despite the challenges, there are a number of ways to address these issues. This includes careful consideration about the time frames of different sourcing options.

Manufacturers in Europe can often take six to eight months if they are producing a large quantity of drugs. Smaller amounts, especially those with good expiry dates, could be completed much quicker, possibly in as little as two weeks if coming from the US.

"You just need to have the experience to make that judgement, and obviously you need vendors with the best contacts all over the place," explained Mattsson.

> "Trial sponsors are increasingly investing in their comparator supply chains, including their own in-house capacities, in an attempt to be first to the market."

Having go-to vendors can be a valuable strategy. "You really want to have a vendor, a very large distributor, who is distributing drugs for manufacturers," said Mattsson. "Or you can pick one locally, but then you have to qualify it. So, we normally use our preferred vendors most of the time."

Building strong relationships through networks, such as the Comparator Network established by non-profit TransCelerate BioPharma, can be hugely beneficial. These allow for the mutual exchange of drugs for clinical trials, help to reduce the costs and make them less complex.

They can also lower the risk of 'unblinding', where the treatment allocation is revealed to participants by ensuring that drugs are used as intended. The documentation provided by the network enhances patient safety as well as reducing the chance for counterfeits to enter the investigational supply chain, which facilitates continuity within the drug supply for trials.

Go big or go home

Sourcing the right comparator drug can involve a worldwide search. Although offering a number of benefits, this process has to be carefully navigated, as emphasised by Christina Chang, vice-president of global clinical development and medical affairs at OBI Pharma, in a previous interview with *World Pharmaceutical Frontiers*.

"The globalisation of clinical trials can present cost savings and advantages for trial sponsors when sourcing from more cost-efficient markets or from a single global supplier," she explained. "But this requires detailed knowledge of the differing regulations specific to countries and also the ability to meet those regulations."

For drugs sourced locally, there are also a number of strategies than can be implemented to maximise efficiencies.

"A local sourcing specialist can liaise directly with the manufacturer at the local level to schedule production runs to meet either short or long-term comparator requests," explained Chang. "This demand planning secures reliability of supply with quality material and can help maintain flexibility of supply should the study be extended."

Sourcing directly from a manufacturer also enables access to large, single lots of the drug with maximum shelf life and specific batch numbers. In addition, this approach minimises resupply costs and avoids any regulatory hurdles when submitting new drug applications. ››

A local sourcing specialist can liase directly with the manufacturer, enabling access to large, single lots of the required drug.

To ensure these benefits are obtained, getting the appropriate paperwork from manufacturers is imperative.

"They can provide full-pedigree documentation reflecting the chain of custody, from the source to the designated point of delivery," said Chang.

A hybrid approach

Sometimes a combined strategy is required, which cannot be achieved by local or global sourcing alone. Drugs are sometimes locked in for hospital use, for example, which can make central sourcing in these areas more difficult.

"Real central sourcing in this context is the hospital pharmacy just picking the drugs at the site of use," explained Mattsson. "In this situation, you may have to source from one vendor and arrange some kind of hybrid model of central and local."

This is fairly common practice, with many companies sourcing and procuring centrally and distributing locally; it's a particularly popular trend in China, Canada and the US.

"You can have the European drugs for use worldwide, and you have to choose Chinese drugs in China, which is very particular and unique to the region," Mattson said.

In these approaches, clear communication is imperative to ensure that there is a mutual understanding of each other's issues. Mattsson holds regular meetings with vendors to check on ongoing orders and requests, and to make sure that manufacturers are on track.

> "Sourcing directly from a manufacturer minimises resupply costs and avoids any regulatory hurdles when submitting new drug applications."

"We have something like three meetings a week – one to check quality and two for sourcing," he explained.

No pain no gain

Of course, the ultimate goal is to get the right drug at the right site at the right time, and in the right quantities. "Nevertheless, with a significant growth in clinical research expected in emerging regions such as Russia, Asia, South America, the Middle East and Africa, sponsors and drug manufacturers must be prepared for the geographical challenges that lie in wait," Chang warns.

If comparators become unavailable during a trial, timelines will be adversely affected and substantial costs will be incurred for the sponsor. The adoption of a transactional approach, where the focus is on sourcing as quickly as possible, will substantially increase the likelihood of this occurring.

The future development of comparator sourcing will remain complex, with a number of different challenges. Clearly, decisions should not be taken lightly. However, with a strategic approach involving a high amount of communication and collaboration, using them can bring huge rewards. ■

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How to navigate the challenges of a changing Chinese market

Rapid economic and demographic changes are causing a boom in the Chinese market for pharmaceuticals, according to Kay-Christian Karstadt, chief operating officer at **Inceptua**. This offers opportunities for pharma companies but the landscape is complex, and understanding the changes will be key to success in the region.

China has become the world's second-largest pharmaceutical market, with enormous potential for international pharma companies. China's senior population is developing increasingly western lifestyles, which, combined with better overall health, has had the positive effect that life expectancies are improving, but associated lifestyle illnesses like heart disease and diabetes are on the rise. This poses a challenge for healthcare services in the country.

The government is already taking measures to develop its healthcare system to handle the increasing demand. The 'Healthy China 2030' plan signalled its commitment to improving the health of the nation, and the plan is supporting the growth of this industry in a number of areas, including pharmaceutical distribution.

As China adapts to its environment, challenges arise for foreign pharma companies that are newly navigating the Chinese pharma market and looking for local partners.

A fragmented market

China's pharmaceutical distribution market is currently dominated by small-scale domestic distributors, often focused only on their local areas. In these regions the top wholesalers hold less than one third of the market share.

Mergers and acquisitions have been encouraged by the Chinese Government. Large wholesalers are absorbing smaller distributors in order to increase their overall market share and strengthen their capabilities in smaller cities and rural areas. This market consolidation is leading to shorter supply chains, better enforcement of industry standards and regulations, as well as reduced costs. Working with a partner that understands this shifting market, and can advise on the best solutions, is key for pharma companies wishing to operate in China.

Reducing risk and costs

A multi-tiered distribution structure means products change hands multiple times before reaching a patient in need. This increases cost and risk, with multiple margins added and increased opportunity for counterfeits to enter the supply chain.

In an effort to reduce the risks and costs, the government has started to implement a two-invoice system: one invoice from the manufacturer to the distributor and one invoice from the distributor to the buyer. Limiting the supply chain length will make the process more transparent. However, foreign pharma companies that need access to a wide range of products will need to partner wisely: a distributor that cannot access the required products will not be able to work with other distributors to increase its sourcing capabilities.

The Shanghai skyline: China is the world's second-largest pharmaceutical market, offering immense potential for international investment.

Logistics challenges

China suffers from an unevenly developed logistics network, mainly due to its vast size and varied geography. Consolidation of distributors will add pressure on existing logistics service providers that are not yet optimised for handling cold chain products, nor for complex inventory and delivery requirements.

Pharma companies are looking to partner with distributors that offer full-service logistics solutions to better control their supply chains and reduce risk. This increased demand is encouraging distribution companies to improve their logistics service offerings.

The landscape for international pharma companies wishing to operate in China is not a simple one, but finding a partner that can help navigate the rapid change and development currently under way will be critical. Early-stage consulting, reliable access to products and full-service logistics solutions will provide the foundations international pharma companies need to make the most of China's opportunities. ■

Further information
Inceptua
www.inceptua.com

New direction

The growth of direct-to-patient (DtP) clinical trial strategies is expected to continue for the foreseeable future. Adopting a DtP approach has the potential to improve recruitment, retention and efficiencies, as well as reduce costs. However, legal and regularity barriers can hinder implementation. Emma Green considers the challenges.

For manufacturers, who can spend anywhere from $161 million to $2 billion to bring a new drug to market, the returns from investing in this important work have been gradually diminishing. Patient recruitment and retention, which cost around $2.3 billion a year, have become major challenges. These issues can cause trials to become longer, more expensive and less statistically robust, as well as result in poor morale among researchers, healthcare providers and patients.

In light of an ageing population, pharmaceutical manufacturers are shifting their focus to researching chronic and degenerative diseases. Resolving recruitment and retention issues in this population has thus become an increasing area of concern. The rapid developments in technology over the past few years have enabled the creation of direct-to-patient (DtP) strategies, which can help to address patient engagement challenges. This approach follows the standard blinding protocols but sends medication directly to the homes of participants. This means that they do not have to travel to medical facilities or wait for services. This convenience can be a key factor in boosting patient recruitment and retention.

Short-sighted

In the traditional trial model, the investigational site plays a central part. All staff involved, including nurses, patients and researchers, must travel to the site. It must also be close to patients because they will be required to visit the site frequently, which can be challenging.

"It can be difficult logistically for patients to attend these appointments, especially if they work or care for family

members," says Deborah Collyar, president of Patient Advocates in Research.

The DtP approach eliminates these issues, and instead they are placed at the centre of the clinical trial process, in line with a more patient-centric model.

"This type of research can make the clinical-trial experience easier for patients and their families, which means they are more likely to join the trial and stay involved with it," explains Collyar.

It is estimated that as many as 50% of site visits could be successfully relocated to a patient's home. In light of the average dropout rate of 30%, DtP strategies are worth serious consideration.

Although not suitable for all clinical trials, they are particularly valuable for research on particular populations.

"They work well for patients who are sicker and older, and in settings where more frequent visits are required," says Collyar. "The DtP approach can also be good for paediatric trials, especially for rare diseases, which tend to have difficulties recruiting enough participants."

Proper planning

The most important part of implementing DtP strategies is getting the initial plan right and ensuring that it is broad enough. This process should involve all stakeholders and clearly define the scope of work, required resources, project time frames and feasibility of practices.

> "It is estimated that as many as 50% of site visits could be successfully relocated to a patient's home."

"A disadvantage is that more time may be needed to set up the trial initially," explains Collyar. "However, upfront planning can help the trial run more smoothly."

Depending on the location of participants, when more home visits are incorporated into trials, nurses or courier drivers may be travelling long distances to a patient's home. Each home visit requires a coordinated approach from all stakeholders to ensure that the medication reaches the patient's home on time, and at the perfect temperature and condition, regardless of the distance travelled. A single temperature excursion or delay in delivery can compromise the life of a patient as well as the entire study.

Sponsors also can face greater transportation costs due to a high volume of small shipments, and the reverse logistics of shippers and biological specimens. Ensuring that the drug is stored properly at the patient location can also be costly and challenging. To address these issues, some companies have started to use small, temperature-and-access-controlled refrigerators in patient's homes. This can help to promote patient adherence as well as prevent medication wastage.

During the planning stage, it is also imperative to establish a strong relationship with a home trial company in order to gain insight into the regulatory landscape. Companies that can offer in-depth knowledge of the countries in which they operate can help to ensure adherence to both trial standards and local market regulations. Both of these can vary considerably from country to country and are subject to change, which makes this insight particularly valuable.

Confidentiality is an important issue to consider because the service provider and the couriers will not be fully trained in good clinical practices (GCP). While almost all of the communication goes through clinical personnel, it is the service provider's responsibility to ensure that the courier complies with the delivery protocol. To achieve good practice in manufacturing and distribution, it is important therefore to not only have the patient's name and address, but also a caregiver's phone number. Ensuring privacy of this information is key.

Collaboration is also extremely important in dealing with complexities. In some cases, patients are just receiving medication. In other cases, their drawn specimens will need to be delivered back to labs for analysis, requiring careful planning and timing. Furthermore, patients are sometimes unwilling or unable to self-administer medication, especially when working with injectable drugs. Coordination with a healthcare professional or carer may therefore be required to administer the drug and/or help with returning the specimen to the lab.

Tracking technology

A number of different technologies are being used to help manage deliveries in trials implementing DtP approaches. These include both GPS and Bluetooth Low Energy. These are helpful in monitoring shipments at each point in the supply chain, including when products are placed in the storage facility or pharmacy, when they are

Case study: Pfizer's REMOTE study

The first virtual clinical trial was Pfizer's Research on Electronic Monitoring of OAB Treatment Experience (REMOTE), conducted in 2011. This pilot study used mobile and web-based technologies to recruit and enrol patients, and collect data without any visits to clinical sites. The trial aimed to evaluate the safety and effectiveness of an overactive bladder treatment. By comparing results from REMOTE with a previously completed trial, sponsors aimed to determine whether a direct-to-patient approach could achieve similar results.

The pilot generated a large amount of interest, but struggled with recruitment issues, patient concerns about confidentiality of data, burdensome online research processes and a lack of human support through a study contact centre. Following feedback from patients, the trial was revamped to include a call centre that could provide support during the initial enrolment steps. This increased recruitment, but due to delays the trial was discontinued.

The REMOTE study demonstrates that despite the capabilities of technology to perform a range of tasks in clinical trials, a lack of human interaction could hinder participant engagement. It is thus important that when implementing DtP strategies that human involvement remains a central aspect of trial design in order to maximise both patient recruitment and retention.

Sending medication directly to the homes of clinical trial participants could boost patient recruitment and retention.

picked up by a driver and when they are delivered to the patient's home.

When using monitoring technologies, it is crucial that they allow for full audit capability to determine whether the drug is usable or not. Currently, technologies are not able to provide in-flight visibility, which would allow for timelier problem resolution to take place in global trials. However, technology is evolving, and airlines are now working closely with device manufacturers to explore data-recording strategies, such as the use of wireless networks on flights.

A DtP approach could also boost supply-chain efficiencies by reducing the number of handoffs and investigator site costs. As patients are not required to visit a particular site, there is often only a single site for managing regulatory submissions. Trials can be managed centrally by a remote-study coordination centre that facilitates all research activities, including recruitment, screening, informed consent, enrolment and data collection. A medical team monitors the health and safety of participants by reviewing all data as reported in real time. By relying on only one site, or a small number of sites for global trials, the DtP approach is highly cost-effective. Research suggests that it could help reduce costs by up to 16% in phase-I trials, by up to 22% in phase-II, 17% in phase-III and by up to 13% in phase-IV.

Another advantage of having a small number of sites is the ability to collect a large amount of data from diverse sources. This is because, unlike site-based studies, data is not collected by investigators during site visits, but instead through the central study coordination centre. This enables data to be obtained from patients themselves, caregivers, healthcare professionals, electronic health records, existing registries, databases, labs and biospecimen repositories.

Depending upon the design of the trial, information collected could include basic demographic information; anthropometric, biological and lab measurements; medical, family, occupational and behavioural histories; disease status and natural history; drug treatment information; quality-of-life; disease-related disability; and treatment satisfaction feedback.

Calling for change

One obstacle when implementing DtP trial strategies is the fear of internal and external change. All companies have established habits, and decision-makers become accustomed to particular budgets, working practices and timelines. Making adjustments to these can be highly challenging, and require a positive and proactive approach. Externally, it can be difficult to navigate relationships with different stakeholders, many of whom may be invested in maintaining the current system of clinical trials. Such issues explain why, despite the rapid technological progress achieved over the past 30 years, many practices within clinical trials have remained relatively unchanged.

As the industry moves towards a more patient-centric approach, the DtP model has become a growing trend in clinical trials. A recent survey projected that DtP trials would increase from 24% of all clinical trials in 2017 to 33% by the middle of 2019. Once viewed as unrealistic due to quality and cost concerns, trials adopting a DtP approach are now viewed as viable and valuable. These strategies are undoubtedly opening up the possibility of more people participating in clinical trials than ever before. They could prove instrumental in boosting recruitment and retention, allowing for more efficient and effective clinical trial procedures.

Despite the fact that applying this approach raises a number of challenges, DtP strategies are clearly here to stay, and require contemplation and collaboration from all clinical-trial stakeholders. ■

Improve pharma R&D efficiency: the need to transform clinical trials

Cost pressures on drug development are driving the search for savings and efficiencies during clinical trials. **ICON** knows why efforts need to be integrated if they are to be effective.

With development cycles becoming longer and longer, trial complexity increasing and greater scrutiny being placed on the economic value of new treatments, pharma R&D business models are under significant pressure to improve efficiency.

In an industry survey of pharmaceutical executives and professionals undertaken by ICON, the challenges most frequently cited are:

- patient enrolment – 56% of survey respondents
- site start-up – 43% of respondents
- regulatory approval delays and changes – 43% of respondents.

These operational issues reflect the difficulty of designing studies that address critical patient and investigator needs, as well as evolving regulations.

Elevating efficiency and enhancing trial savings

Patient identification and recruitment, and risk-based approaches to study monitoring, are expected to have the most impact in transforming the efficiency, speed and productivity of clinical development.

Declining pharmaceutical R&D efficiency and the resulting deterioration in return on investment is largely driven by lengthening development cycles. These, in turn, typically involve increasing trial complexity and regulatory approval delays. These complexities and delays are symptomatic of deep structural changes in therapeutic markets that conventional clinical trials are simply not designed to address. These changes include smaller targets, personalised medicine and value-based care.

Driven by scientific advances in areas including biochemistry, genomics and biomarkers, the market for new therapies has moved towards targeted therapies and orphan indications. The smaller potential markets mean the R&D enterprise – and clinical trial designs and procedures – must be tightly focused on patient needs, relevant clinical and research expertise, and maximising efficiency in demonstrating safety and efficacy.

New product offerings target specific biomarkers, such as biologic chemotherapy agents, or even individual patients, such as CAR-T immunotherapy. Similarly, therapies that combine mobile sensors and devices with drugs and delivery devices require evidence of real-world efficacy and safety that cannot be generated in a controlled environment.

In addition to efficacy and safety, clinical trials increasingly must demonstrate a meaningful impact on patients' lives. This is particularly true for high-cost therapies targeting smaller patient groups. Screening patients to identify potentially better responders and linking payments to individual patient outcomes are among the measures payers are negotiating with sponsors to ensure they are getting value for the money they spend.

The impact of digital disruption

Emerging technology capabilities are expected to play a vital role in transforming clinical trials – including leveraging big data and predictive analytics. Integrating study and electronic health records may increase data collection reach and efficiency, and help better integrate trials into clinical practice.

Patient-focused technologies, including mobile sensors, smartphone apps and telemedicine, are seen as ways to collect richer patient data, develop new end points and help design novel kinds of trials that may better demonstrate real-world clinical and functional value.

While the technical challenges of applying new technologies – such as big data, AI, and wearables and mobile devices – to clinical trials are significant, their value already has been confirmed in many studies, saving millions in development costs. They make possible innovations that are fundamental for transforming clinical trials, such as seamlessly combining phase I and II of clinical trials, developing novel patient-centred end points, and collecting and analysing real-world data.

A holistic, integrated approach to transformation

The cost pressures on drug development are driving the search for savings. While large-scale operational efficiencies are being instituted in many pharmaceutical organisations, efforts need to be integrated if they are to be effective.

There is a growing understanding that improving R&D efficiency and return on investment will require a holistic approach to transforming trials, rethinking and redesigning the trial product itself and the enterprise that supports trials from the ground up. ICON is addressing this need through its Transforming Trials initiative. ■

Further information
ICON
www.iconplc.com/pharma

Using social media for clinical trial recruitment

MESM provides medical equipment solutions and services for the clinical trials industry. Here, it examines how social media can help with participant recruitment, and provides information on how companies can get started in implementing a suitable social media recruitment strategy.

Over the past ten years, the rapid growth and use of social media networks by the general population has created a powerful new tool for pharmaceutical companies and clinical research organisations (CROs) to engage with patients and recruit them for clinical trials. CROs and pharmaceutical study sponsors are still learning how to effectively use social and digital media as part of their participant recruitment strategies.

This article discusses the benefits of social media for patient recruitment, examples of how social media can accelerate recruitment, and some tips for approaching organic and paid social media recruitment campaigns.

Social media's advantages for patient recruitment

Today, new and innovative methods to recruit clinical study participants are urgently needed due to the rising cost of conducting clinical research and the increasing focus on developing therapies for more niche populations.

Using social media to recruit clinical study participants offers key advantages compared with traditional recruitment methods such as physician recommendation and TV, radio and newspaper advertising. Because of its low cost and ability to reach a diverse and broad audience, social media can be a cost-effective approach. Social media has also been shown to recruit 'hard-to-reach' groups that cannot be easily accessed through traditional methods, such as low-income populations, adolescents and young adults.

The use of social media can also reduce recruitment time by allowing clinical research teams to identify and engage with people in specific demographic groups who would be more relevant subjects for their particular clinical trials. Connecting with patients through social media can allow researchers to design more patient-centric trials by listening to patient groups and understanding what they are seeking from clinical research.

Diverse platforms and demographics

Social media platforms can be broken down by key demographic factors, including age, gender and country. Analysing these online demographic groups can help clinical researchers to identify the right platforms to target potential study participants. According to results from the Pew Research Center survey, issued in November 2016, the use of Facebook by US adults continues to increase, while the adoption of other social media platforms remains stable. In the US, 80% of internet users – 68% of all US adults – use Facebook. In second place are Instagram and Pinterest, while LinkedIn and Twitter show the least use.

Patient advocacy groups offer new opportunities for clinical study recruitment. These groups often have a very active social media presence. Many have their own websites, Facebook and Twitter pages, and discussion boards. Patient advocacy groups associated with rare diseases tend to have online members who are very engaged, and more likely to be potential study subjects.

It is important for CROs and pharmaceutical study sponsors to establish relationships with these associations by regularly informing them about new clinical trials at each stage, including a trial's recruitment, study progress and outcomes. Keeping in touch with patients at all stages can make them feel more involved with the clinical study process, while also allowing clinical researchers to reach new target audiences. Sponsors can have press releases to post on patient advocacy websites, provide links to relevant information about studies, or use newsletters to share information about upcoming trials or the results of recently completed studies.

Some pharmaceutical sponsors are partnering with patient advocacy groups to increase patient awareness and recruitment for clinical trials. For example, MyHealthTeams is a website that hosts social networks for diseases such as epilepsy, Crohn's and chronic obstructive pulmonary disease (COPD). In 2014, MyHealthTeams partnered with Biogen Idec to screen and recruit patients for inclusion in Biogen clinical trials. Following this agreement, Biogen was able to progress from screening only six patients a week to screening around 400 patients per week.

Accelerating online awareness of clinical studies

Other sponsor companies are using digital advertising campaigns and videos to accelerate patient recruitment. In one example, a pharmaceutical manufacturer was able to fully enrol a clinical trial for non-small cell lung cancer (NSCLC) in just four months, using digital and social media as a recruitment tool. They used a high-quality website as the main hub, directing people there using ads on Google and Facebook and through an introductory video on YouTube. The team saw traffic to the trial's website increase by 6,474% by the third month, resulting in close to 70,000 website visitors who looked at one or two pages of content. This demonstrates the power social media can have to reach people and improve the process of recruitment, when used effectively.

Healthcare professionals are also leading the way in initiating social media recruitment. In 2014, the hashtag #WhyWeDoResearch started as a twitter campaign aimed at raising research awareness among healthcare professionals, patients and public. Within five months of its launch, this Twitter campaign reached 14 countries and gained 2,364 participants. Among other community engagement activities, the #WhyWeDoResearch website now posts opportunities for patients and the public who are looking to participate in clinical studies.

Tips for social media recruitment campaigns

There is more than one way to approach using social media for recruitment. Social media platforms can be used as advertising tools, where you can pay (usually by number of clicks or impressions) to promote posts to users within specified target demographics. However, it is essential to understand how the use of paid social media promotion is regulated in the locations where campaigns are being run. Additionally, all copy used to recruit patients should be approved in advance and kept on record for future reference. For example, if a study is subject to approval by an institutional review board (IRB), the board will typically review all the materials used for recruitment, and this will include paid social media posts.

On the other hand, social media can be used organically, without running paid placements. It's possible to run accounts, pages and engage with social media communities without paying to reach people. Although finding potential participants for a trial this way may take more time and commitment, there are ways to make this work, and a combination of both paid and organic may be the optimal approach. It may be most effective to run ongoing organic social media activity to build long-term relationships, with paid campaigns used at key recruitment moments, for example.

Some approaches to make the most of organic social media activity include:

- reviewing digital channels and social media sites to discover targeted patient audience and caregivers online
- monitoring and analysing current online discussions on a specific disease area to learn about the issues that the patient audience and caregivers are discussing
- studying users' language, including the specific words and phrases they use to describe their symptoms. This 'patient speak' can be used in social media content, rather than less accessible medical terms
- identifying key hashtags and regular online chats for use in conversations, to discover target audiences and build a relationship with key contacts such as patient organisations.

CROs and pharmaceutical companies are increasingly recognising the value of social and digital media for engaging with patients online and recruiting them for clinical studies. However, no single social media platform will suit every patient or clinical trial. As such, social media should be used as a supplement to other available recruitment methods. A recommended strategy would be to integrate social media into already existing print, radio and TV ads, along with physician referral. Using a combination of these methods is likely to play a key role in the future success of clinical trial recruitment. ■

Further information
MESM
www.mesm.com

Strong ties

Social media is a powerful tool for patient recruitment, providing a valuable addition to more traditional methods. It can be harnessed to build strong relationships between sponsors, site physicians and patients that begin before the trial and can last all the way through to the next. **Wolfgang Eglmeier** of Witten/Herdecke University talks to Emma Green about how to optimise social media strategies to foster these connections.

The use of social media has massively increased in recent years and it is estimated that over three billion people worldwide are currently engaging. No longer merely a tool for personal communication, it is now commonly used to help achieve business goals – and offers huge potential for the recruitment and retention of patients in clinical trials. However, despite its value, social media is a highly underutilised strategy by pharmaceutical companies. A report by Fisher BioServices found only 11% of trials leverage social media for recruitment. In light of the ongoing challenges in obtaining sufficient participant numbers for trials, there's never been a better time to log on.

Before using social media strategies to engage people in clinical trials, it is imperative to understand the reasons people choose to participate or not. Research published in *Clinical Trials Perspective* has identified seven different types of patients and their motivation for becoming involved in trials. 'Innovative patients', for example, look for new developments and technologies. 'Desperate patients' search for any available treatment options. 'Health-conscious patients' are keen to get a high level of attention from physicians.

'Economic patients' want to receive free treatment and support. 'Impatient patients' desire fast access to physicians and new information. 'Altruistic patients' want to do something good for society. Finally, 'bored patients' are keen to do something unusual.

People often have more than one of these intentions and their reasons can change over time. For example, those who are younger tend to be more innovative, desperate or impatient. The elderly are more likely to be health conscious, economic or altruistic. Social media can be used to address the different motivations of these patients, particularly those who are younger and tend to be more engaged with technology.

There are also a number of reasons that patients may choose not to participate in clinical trials, including a lack of information about what is involved. Some may not consider their involvement to be beneficial. Others consider participation to be cumbersome and not worth their time. Sometimes, people would like to be involved but do not consider themselves to be eligible due to poorly communicated exclusion and inclusion criteria.

Wolfgang Eglmeier, head of the Centre for Clinical Trials at Witten/Herdecke University, has 25 years of pharmaceutical industry experience, and strongly believes that social media can help to overcome these issues. However, this demands a strategic and long-term approach, which should be implemented before the trial recruitment phase even begins.

Centre of attention

Ensuring that a trial is patient-centred is key to boosting willingness to participate, but this rarely happens in the design phase.

"Clinical trials are often planned in some remote office and there is no real focus on patients," says Eglmeier. "It is sometimes forgotten that a person has to buy into the study and dedicate part of their lives to a trial."

Asking patients directly about their inclination to become involved can help to pre-empt potential barriers to participation. This includes questions such as: "What are their needs?", "What are they willing to devote to a clinical trial?", "What can they do?" and "Is a clinical trial really suited to them or is it too cumbersome?" Having this dialogue is difficult when using traditional methods, whereas social media provides the ability to reach a large audience and gain feedback quickly.

> "Social media can be used to address the different motivations of patients, particularly those who are younger and tend to be more engaged with technology."

These platforms can also be used to provide patients with material to help them with their decision to participate.

"Things like Wikipedia or YouTube can be helpful for giving out information," explains Eglmeier. "You can use these for training materials for the disease, the drug being used and also for self-assessments."

Rules of engagement

Although there are clear benefits to using social media for patient recruitment, it is no easy ride.

"It's a lot of investment, in terms of money, knowledge, experience and time," admits Eglmeier.

Data privacy is another big hurdle to navigate, especially in the EU. The governance within the EU makes it difficult to collect personal data. This also threatens patient confidentiality, so a lot of planning is required to ensure that these challenges are anticipated and addressed. This is not only a problem to do with patients.

"The other issue is confidentiality of the company's data," Eglmeier notes. "This should also be kept private and should not flow out to competitors, for example."

However, such challenges are not insurmountable. Patient organisations can be helpful throughout the recruitment process. However, it is imperative to be honest and open with them from the start about who is behind the trial.

Engaging with these groups can also be highly cost-effective.

"At the beginning, these patient support groups are doing the job for you and can even provide you data later on," explains Eglmeier. "Normally, you have to pay for data."

Building connections with these various groups does require careful management, however.

"You need a contract, a clear share of responsibilities and information about the purpose of the data being collected," says Eglmeier.

Information overload

In addition to finding fruitful avenues to engage with patients, providing sufficient information about the trial itself is paramount. This includes the provision of contact information; inclusion and exclusion criteria; details about how long it will take; what is involved; and whether there any costs or benefits from participating.

However, providing information must be done with caution.

"The more information that you provide to a patient, the more you get into a situation where you are using software that would be categorised as a medical device," warns Eglmeier. This requires additional rules to be met.

Software as a medical device is defined by the International Medical Device Regulators Forum (IMDRF) as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device".

Ensuring that information-sharing does not fall within this remit is key to avoid facing delays or penalties in the recruitment process.

Navigating miscommunication is another important issue when using social media. ››

Social media can be used to recruit people for a clinical trial and maintain engagement after it has concluded.

"You should never give the impression that a person is entitled to participate in a trial – the final decision is made by a physician," warns Eglmeier. "Patients can decide whether they want to participate but cannot force themselves in."

Different strokes

It is also important to consider those who may be excluded when using social media.

Patterns of engagement have also been shown to differ considerably across diseases.

"Patients with cancer or diabetes are more involved with social media because they are long term diseases," explains Eglmeier. "Nobody is running around on social media trying to get information if you just have something like flu."

> "You should never give the impression that a person is entitled to participate in a trial – the final decision is made by the physician."

For this reason, these online platforms cannot yet replace more traditional recruitment methods.

"It is an add-on," says Eglmeier. "There are still constraints; for example, the informed consent procedure has to be done by a human being."

Another limitation is difficulty in targeting population groups who are less active on these platforms.

"Social media often only addresses more technology-prone people," says Eglmeier. "People in their 80s will likely never touch a smartphone so it's difficult to contact those people."

Geographical location can also affect social media activity and willingness to participate in a clinical trial. In the UK and a number of countries in Europe, high-quality medical care can be obtained at no or very little cost. However, in countries like the US, it can be expensive for patients, which can make participating in a trial a more attractive option.

Mind the gap

Once a trial is over, participants tend to be forgotten about. Social media provides a useful way of maintaining engagement, which can aid recruitment for future trials. Giving feedback to participants about the trial is particularly valuable.

"At the end it is quite helpful to spread information about what really happened, the number of patients, how many received the drug and what the outcome was," explains Eglmeier. "That gives them an appreciation, not just for the drug, but for the whole trial."

However, this kind of communication rarely occurs in an effective or timely way.

"Currently, pharma companies collect the data, run the stats, publish the results and give information to physicians who supposedly give that back to the patient," says Eglmeier.

This process can last three to four years after the trial has ended.

"In some cases, the person has already died by that time point, if they have a terminal disease," says Eglmeier.

Being forward-thinking can really pay off. For example, social media can be used to promote participation between trials.

"We have this wonderful phrase from our national soccer team '*Nach dem Spiel ist vor dem Spiel*' which translates to 'after the game is before the game'," says Eglmeier. "In clinical trials, we can think about this as 'after the trial is before the next trial'." ■

Ride the tidal wave of data

The variety and quantity of data available for clinical trials is greater than ever before. While this promises huge benefits in terms of monitoring subjects and measuring results, more information doesn't always translate to more knowledge. **Kumar Komuravelli**, director of clinical data management at Mallinckrodt Pharmaceuticals, tells Grace Allen about the challenges facing clinical data management and how these developments can be capitalised upon.

It is said that of all the data in the world, 90% originated in the past two years. According to the 2018 'Dojo Data Never Sleeps' report, by 2020 1.7MB of data will be produced every second for every living person on earth. Every minute, over 3.8 million Google searches are made, nearly 160 million emails are sent and 473,400 tweets posted.

This avalanche of information is making itself felt in the conduct of clinical trials, offering huge potential for improvements and also putting increasing pressure on the management of clinical data. It is not only growing by volume: once largely limited to

case report forms, the sources of clinical data are multiplying, with paper and electronic case report forms (CRFs) joined by electronic medical records (EMRs), electronic patient reported outcomes (ePRO) and a host of eSource data, captured straight from its electronic point of origin.

Predictions suggest that the proportion of non-CRF data will continue to rise. The 'Tufts–Veeva 2017 eClinical Landscape Study' found that, while eCRFs remain the source of the great majority of clinical trial data by volume (77.5%), the survey's respondents expected their use of other sources to increase. 69.7% foresaw an increase in the overall number of sources they would make use of in the near future, while 91.6% predicted they would be using smartphone data in three years' time, up from 44.8% incorporating it at present.

> "The key to successful incorporation of IoT and eSource information is a strong understanding in the trial design phase of the purpose of each element."

The sheer quantity of data points available from the development of internet of things (IoT)-enabled medical devices and applications brings opportunities and challenges. Smartphones, smartwatches, patches and other trackers can record variables such as heart rate, blood glucose level and blood pressure continuously and accurately, while eSource technology allows this to be collected in real time and with no potential errors arising from transcription. The use of wearables can streamline the conduct of a trial and extend its reach to wider demographics, and more data and greater data integrity give a clearer picture of a trial subject than ever before.

Not all data is useful data

However, just because vast wealth in terms of data points and volume is available doesn't mean that it should all be collected.

"Do you really want to capture the blood pressure or heart rate every minute?" asks Kumar Komuravelli, director of clinical data management at Mallinckrodt Pharmaceuticals. "That's a humungous amount of data. Even every hour – that's still a lot of data you're conducting to your trials. Is it useful?"

Komuravelli emphasises that the key to successful incorporation of IoT and eSource information is a strong understanding in the trial design phase of the purpose of each element.

"In data collection, the first question you need to ask is what you're going to do with this data," he says. "You need to have a road map of where you're going to capture what data."

In the end, collecting data that offers no value to the purpose of the trial creates unnecessary complexity.

Further complication is created by the disparate nature of much of the data now available, which can range from numerical values to medical images, genomic data and open text responses: these need significant manipulation to enable it to interact in a cohesive manner. A 2018 study carried out by Pharma Intelligence for Oracle Health Sciences found that over a quarter of respondents feared that the cost of conducting trials would be significantly increased due to the need to collect and manage new data types.

Clinical and metadata repositories

The answer to this in the recent past has been the enterprise data warehouse, which combines data extracted from a range of sources together to allow for analysis. Now, however, data managers are combining or replacing this method with a clinical data repository (CDR), which allows the data to be used flexibly for multiple functions, or data lake solutions, which maintain the data in its original form.

By keeping the data in its source format, a data lake does not facilitate easy extraction of analytics and requires skilled analysts to interpret the information it contains. However, this approach reduces any errors or compromises that may arise from forcing disparate information into a proscribed record format, allows for greater detail to be preserved, and means that the requirements of the data can have flexibility.

In addition – and of great significance as the quantity of clinical trial data continues to rise – the data lake is a streamlined solution. While much time must be dedicated to the design of an enterprise data warehouse and to the entry of information from the original source, this is eliminated when it is kept in a copy of the original in a data lake.

As data multiplies, the role of metadata – the information that places each data point in its context – is vital. This is particularly true for a data lake or clinical data repository where well-defined metadata is needed to locate and analyse the contents. While metadata is another level of data to be managed, its creation can be automated and it can be housed in a metadata repository (MDR). Its use can lead to numerous advantages, one of which is for the review of data in order to develop future trials.

"It's definitely useful," Komuravelli says. "When you have these data structures – like MDR – developed, and then the actual clinical data is captured in a CDR model, it's easy to pool the data, pull the data and review the data, and look at it from different angles for future studies for the companies. So what happened – why did this fail?"

In addition, metadata proves useful in the regulation of clinical trials. It makes

Well-defined metadeta offers numerous advantages, including making it easier to review data in order to develop future clinical trials.

each data point traceable throughout the trial lifetime, through any change in format, and means any request for information from a regulator is easy to comply with. Nevertheless, the cost of staying up to date can cause issues.

"This is an evolving technology regarding MDR from the past few years," Komuravelli says. "The bigger companies have some rules and guidelines for what to do with it and how to use it, but I don't think the midsize and smaller companies have that knowledge – the technology is expensive for smaller players."

The impact of adaptive trial design

However, Komuravelli suggests that these companies can identify opportunities through collaboration, sharing knowledge on metadata processes to bring efficiencies into their work.

"Trying to use two different databases for two different cohorts is not the right thing to do; it's a headache and it's not the best practice," Komuravelli says. "You need to consider the overall picture; what happens with the destination or study data page, how you want to capture the contents, what happens with the medical history and arrivals.

"You need to think, how can I design the study expecting that things will change over the period of the trial from cohort one to cohort two?"

> "Trying to use two different databases for two different cohorts is not the right thing to do; it's a headache and it's not the best practice."

Technological advances, such as artificial intelligence and machine learning facilitated by cloud computing and robotic automation offer avenues for managing this ocean of data, but the industry has to practice caution.

"The biotech industry moves slower in technology, the reason being that we are a regulated industry," Komuravelli explains. "We're constantly monitored by the regulatory authorities and we're dealing with drugs: we're conducting the clinical trials on patients, so you have to take this into serious consideration."

Nevertheless, the industry is awake to the need to use state-of-the art methods to manage data.

"On one side there is the regulation, and on the other is the technology, but at the end of the day the technology wants to help you," Komuravelli says. "As long as we know what we are doing, the technology definitely helps."

One thing is clear: innovative, flexible and reliable data management techniques have never been more important. ■

EDGE - the cloud-based system for overseeing clinical studies in real time from anywhere in the world.

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The EDGE system, developed by the Clinical Informatics Research Unit at the **University of Southampton**, is already embedded across 80% of the NHS within the UK and is quickly becoming a front runner for clinical trial management systems internationally. EDGE provides users with faster access to real-time data and complete study oversight from start to finish.

The world of clinical research can be a challenging one, no matter what stage of the research process you work in, whether that is at site or sponsor level. Historically, this was mainly due to research being conducted in silos – some people were not willing to share information and collaborate. Things certainly changed for the better when the Clinical Informatics Research Unit (CIRU) took the issue into their own hands and developed EDGE.

Subscribing to EDGE ensures that the organisation responsible for the study can oversee the data that they need to monitor and track study performance.

The power of data

Data can be a powerful thing, especially when it is kept accurate and made easily accessible to those who require it. EDGE promotes the input of accurate, efficient data and removes the duplication of efforts for all those involved in a research study. The cloud-based system fully supports data sharing and collaboration among sites that are undergoing research. This collaborative approach allows a much quicker, more efficient research process. It reduces the burden of research administration, therefore giving staff more time for the things that really matter: patient care and patient experience.

> "Pharmaceutical companies traditionally 'inbound' technology into sites to manage their specific trials, but now the capability exists to subscribe to the embedded system in place to monitor specific studies in the UK."
>
> **– Professor James Batchelor**

80% of the NHS

The process of research is made so much easier when everyone involved is working in the same place, sharing information and best practice. The EDGE system is already used successfully among 80% of the NHS, across Canada, Belgium and further emerging global markets. Professor James Batchelor, director of CIRU, notes, "Pharmaceutical companies traditionally 'inbound' technology into sites to manage their specific trials, but now the capability exists to subscribe to the embedded system in place to monitor specific studies in the UK." Subscribing to EDGE ensures that the organisation responsible for the study can oversee the data that they need to monitor and track study performance. This data already exists in EDGE.

Adaptability and flexibility

Systems that can be easily adaptable and flexible to meet users' needs are key elements to real success. EDGE was developed to work for any organisation, large or small, commercial or non-commercial. CIRU develops great relationships with its customers to ensure that they make the most out of EDGE. It promotes idea sharing, which leads to further enhancement of the system, providing its users with up-to-date functionality which they can use to improve their research management.

Part of the community

As a strong believer in collaboration, CIRU actively engages with its user base, assisting with skill and expertise development. Becoming a member of the ever-growing EDGE community saves money on the costly implementation and training that often occurs when it comes to implementing a brand-new research system into a site. It also provides that all-important communication channel between the sponsor and the staff, who are at the forefront of clinical research. Subscribing to a system that is already deeply embedded and understood by thousands of research staff can build further collaborations and partnerships among the different industries, which overall will create a smarter, more efficient way of working. ■

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Cool runnings

With the stakes being so high for cold chain, finding new ways to maximise efficiencies and prevent revenue losses is key. Digitisation is a cost-effective option with huge potential, but it remains underutilised within the industry. Abi Millar investigates how to successfully harness these technologies to optimise procedures.

The pharmaceutical supply chain is growing more complex. As the industry becomes increasingly globalised, the path from production line to patient is often something of a winding road, with a large number of different stakeholders involved along the way.

Most obviously, this can pose challenges when it comes to supply chain integrity and transparency. However, it can also lead to issues with product quality. Since many pharmaceutical products need to be maintained within a very particular temperature range, pharma logistics providers face considerations rarely encountered in other industries.

This is more the case than ever as the industry moves towards biologics and biosimilars. According to a recent report by Research and Markets, the biologics market was valued at $254.9 billion in 2017, and is expected to reach $580.5 billion by 2026 (a CAGR of 9.5%). With around 800 new biologics products in the pipeline, there is no going back to an era of small molecule drugs.

A sensitive subject

Most of the time, biological products are very sensitive to environmental conditions, and require very specific

storage and handling procedures, as indicated in their product labelling. Many need to be maintained within a 2–8°C temperature range, but others will require even colder (or cryogenic) storage.

If these temperatures are not maintained, the consequences can be dire. Depending on the product, deterioration can happen fairly rapidly, meaning the product becomes unusable. It might lead, for instance, to an increase in impurities, a separation of layers in liquid products, or change in the dissolution pattern of solid dosage.

Since many of these products are very expensive, temperature excursions can cause severe revenue losses for pharma companies. The Centres for Disease Control and Prevention (CDC) estimates that $300-million worth of vaccines alone are destroyed each year due to improper storage and transportation.

Cold chain logistics, then, is set to dominate industry discussions for years to come. According to *Pharmaceutical Commerce*, the 2018 market for pharma cold chain logistics stands at $15 billion, and is growing a staggering four times as fast as non-cold chain logistics.

"The rule of thumb for many years now has been that the sales volume of temperature-controlled products grows at twice the rate of pharma overall, and that is continuing for the near term," said Nick Basta, editor of *Pharmaceutical Commerce*.

Controlling the costs

The question for pharma companies is how they can best protect these products without breaking the bank. Naturally, it costs more to keep products cold than it does to keep them at uncontrolled ambient temperatures (out of that $15-billion figure, the costs of special packaging/instrumentation are estimated at $4.4 billion). It can, therefore, be seen that there is mounting interest in techniques that will save money – specifically cold chain digitisation.

To date, digitisation – which essentially means harnessing digital technologies – remains underexplored within the industry, and this doesn't just apply within logistics. According to research by McKinsey, the pharma industry ranks in the bottom third of industries when it comes to its 'digital quotient'. In fact, a certain aversion to new technologies is evident even within R&D.

Within the supply chain specifically, there is clearly a long way to go.

The need for speed

One obvious contribution of digitisation is GPS/GSM-enabled sensors to monitor temperatures. These are relatively small so can easily be placed on a pallet or box, and can provide live temperature readings throughout the cold chain.

At a minimum, this allows for easy identification of shipments that have fallen outside the required range for long enough to be considered spoiled and be removed from the supply chain at their end destination. Better yet, some sensors are able to provide more timely alerts about temperatures trending out of range and remedial action can be taken to prevent spoilage.

> "The Centres for Disease Control and Prevention (CDC) estimates that $300 million worth of vaccines alone are destroyed each year due to improper storage and transportation."

Even armed with real-time alerts, however, a cold chain manager may not be able to obtain the necessary resources fast enough to maintain product quality. It is thus imperative to be proactive rather than reactive along the cold chain. This is where predictive analytics can be hugely valuable.

Using this technology provides the ability to look ahead at the scheduled route of a shipment and identify potential issues before they occur. By plotting the forecasted temperature along the predicted location of a conveyance over time, a digital supply chain solution could highlight risks before the shipment even departs. The sensor can then make recommendations based upon these insights to minimise losses. This might include removing one type of product and shipping the remainder, which will be unaffected by the anticipated conditions. Alternatively, another route with more favourable temperatures may be suggested.

One concrete example of a company using digitisation effectively is Merck KGaA. Harmonised, real-time information is obtained about everything from supply chain performance and stock-keeping units to data collected from the company's ERP in order to optimise its operations. By placing sensors along the cold chain that gather data about inventory distribution practices and availability for every product, high end-to-end visibility is achieved. Machine technologies are then used to help with tracking and planning for different types of products.

This technology enables orders to be processed in the shortest time possible as a result of shifting production or materials to different locations as required. The analytics and algorithms applied to the data provide the ability to forecast more accurately than traditional methods 80% of the time, according to an article by *Pharmaceutical Manufacturing*.

Signed and sealed

Delivery can also be enhanced through the use of digital technologies. Networks of drones can provide support for last-mile logistics, which is especially valuable within rural locations. Despite a high level of government scrutiny and regulation, these are already beginning to be implemented within the industry.

In a 2017 report by Pharma Logistics IQ, Cathy Robertson of Logistics and Trends LLC described the way in which drones are currently being used in Africa for medical deliveries. Due to the speed of the technology, optimal temperatures for both

Networks of drones can provide support for last-mile logistics, and are already beginning to be implemented within the industry.

blood and pharmaceuticals can be maintained all the way to the hospital. They do not even have to land; the supplies fall from low altitudes in small paper parachutes. The drones then return to a home base, where they are prepared for a new mission by swapping their batteries and inserting a SIM card containing a new flight plan into them.

This technology is not only being implemented in developing markets. In the US, NASA partnered with a drone start-up business to deliver to a clinic in Virginia. The entire process took around two hours, beginning with the supplies being separated into smaller packages, before getting transported by the drone and then being lowered to the ground via tether to be received by healthcare professionals.

Drones are also being tested in Europe, which includes the integration of biologistic isothermal packaging for temperature control for in-flight monitoring along a predefined and programmed route, directed by longitude and latitude coordinates.

There are challenges with this technology, such as how to share air space with larger aircraft, as well as issues around security and privacy. However, the potential of drones to enhance efficiencies cannot be underestimated. Robertson describes them as the 'secret sauce' within the cold chain.

> "By placing sensors along the cold chain that gather data about inventory distribution practices and availability for every product, high end-to-end visibility is achieved."

Turning the tide

With an increasing amount of digitisation within the industry, the role of the pharma supply chain professional is evolving. The skill sets required to successfully implement these technologies are very different to those in a traditional work environment. Successful adaption will demand training and reorganisation, as well as cultural change.

The enhanced capabilities of these new technologies will also ameliorate the need for certain jobs. For example, automation is likely to replace a lot of handling staff and local 3D printing could significantly reduce the need for finished-goods transportation.

However, digitisation cannot replace all jobs across the cold chain.

"At the end of the day, algorithms are ultimately written by humans and AI is still a long way from replicating the human nuancing, reasoning, interpretation, intuition, contextual awareness and other qualities of cognitive intelligence," said Alan Kennedy, of Team-Up Global, in the Pharma Logistics IQ report.

Although relatively new to pharma, these technologies are already being widely used elsewhere. This is why the supply chain today remains relatively inefficient in comparison with those in other sectors. Embracing digitisation provides the opportunity to level the playing field and truly embody industry 4.0. ■

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The company founder Cem Kolak says; "although our life standards are getting better and human life is getting longer within the developing technology, some cruel diseases may still take our loved ones apart from us. As BL Turkey, our job is not only about sending and receiving shipments but also we make a contribution in the process of cure development that saves human life. In other words **we serve with passion for creating a better life.**

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The importance of effective cold chain storage and distribution cannot be overstated when dispensing biologics to patients. **PCI Clinical Services** takes this issue very seriously, conducting rigorous testing on shipper performance to ensure reliable shipments

Patient safety is the priority of every clinical trial. It is vital that the investigational medicine dispensed to the patient is in perfect condition, whatever the storage and distribution challenges.

Many biologics have stringent stability protocols dictating the acceptable storage temperature range to ensure the drug remains safe and effective. As such, it is critical that trial sponsors consider many factors to control drug temperature conditions throughout the supply chain.

From point of manufacture to delivery to the patient, the drug will be exposed to a multitude of environments during its many stops in the supply chain – such as transit to packaging site, packaging and labelling, shipment to storage facility, storage, shipment to depot, shipment to final destination and storage at investigational site.

Traditional USB temperature monitors enable sponsors to identify any excursions that may occur during shipment. These monitors prove especially useful once in storage at clinical centres or research hospitals; site staff can keep monitors with investigational medicines and frequently check for any temperature excursions.

Real-time analysis

When thinking of more sophisticated, real-time data collection monitors, the real question is what strategies can we use if an excursion is about to happen? In many instances, the potential benefit is insufficient to justify the expense; there may not be enough time or resources to mitigate the excursion before it happens.

The technology of real-time temperature monitoring – while impressive – will not prevent an excursion from happening, but can be beneficial if there are protocols mitigating the consequences of an in-transit excursion. Once a problem is detected, the options are limited depending on where the shipment is located. Either a fresh shipment can be issued to replace the suspect product, or it can be rerouted back to the origin. However, the latter option may not be enough to save the shipment, often invaluable IMP with limited availability.

To ensure reliable shipments, PCI Clinical Services has enabled a higher standard for shipper qualifications, testing shipper performance against extreme temperature conditions that are much more intense than the industry standard requirements. Once a shipment leaves the origin, the shipper will face an array of environmental conditions depending on weather and various global geographies. For example, a winter profile will account for extreme low temperatures on the tarmac, as well as above average hot temperatures at the destination location that may be nearer the equator. A second profile for summer would account for a short period of mild environmental temperature when in flight and even higher temperatures throughout ground transit.

The shipper is chosen based on the weather forecast on the day of dispatch, and has a packaging configuration and cooling method to keep the drug on temperature, whether it be a water-based gel, phase change or dry ice. The chosen configuration will mitigate any environmental risk posed to the investigational product inside.

Limitations of kitting

When considering clinical trials in geographies with limited storage facilities, a common occurrence in Europe (where hospitals in urban areas are older and have tight quarters), it is important to consider package design. The growing popularity of kitting may cause the investigator difficulty once on-site, where storage space – especially refrigerated storage – is scarce. The kit may add additional, unnecessary bulk if there are items that do not require temperature control or monitoring.

At PCI, the ideal direction is to care for cold chain products in a specific temperature-controlled environment and handle ancillary items separately to optimally use valuable and limited cold storage. For example, adding syringes and needles to a kit may look nice and add convenience, but kitting them together is not recommended where storage facilities are in high demand. This will also save the sponsor the cost of cold chain storage and distribution for items not requiring those conditions.

Keeping biologics safe and effective is the highest priority. It is important to consider traditional and non-traditional methods to mitigate every possible risk to the product and patient. ■

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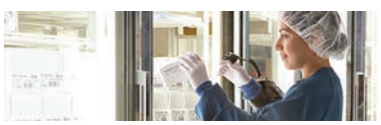

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Safety and security in the last mile

Softbox Systems is an award-winning temperature-control packaging company that has been designing high-performance solutions for over 20 years. Clive Bryant, senior global business development director at Softbox, talks about how the company's new product innovations now allow clinical trial medicines to be protected in the crucial last leg of their journey.

Most of us follow a well-trodden path when it comes to getting the medicine we need: doctor, prescription, pharmacy, home. On a personal level, we know the drill. But through the eyes of the industry, the continued expansion of biologics – coupled with a health sector that's gradually metamorphosing into a more patient-centric entity – means that this process is under scrutiny as it becomes subjected to new pressures and demands.

The area throwing up some considerable investigation is referred to as 'last mile'. While there is some debate on how to interpret this terminology, in essence it refers to moving products from either the depot or clinical investigator to a person's home. But what is behind the surge in interest around this area of logistics?

The biologics explosion

Nowhere is the issue of last mile transportation more pronounced than in the processes that support clinical trials. Vaccines, drugs and other biologics have revolutionised the treatment of patients suffering from some of the most debilitating and life-threatening diseases on the planet. They are the lifeblood of the industry and a lifeline to people in need.

Biologics is the fastest-growing sector in the pharmaceutical business, with total revenues reaching up to $240 billion in 2017. And it's showing no signs of letting up; a figure of around $375 billion is being projected for 2022. In fact, since 1995, the applications for biotech patents have increased by 25% every year. While according to Clinicaltrials.gov, there are nearly 265,000 clinical trial studies currently registered globally, a figure that was just 65,000 only ten years ago.

This rapid growth can be attributed largely to the increased capacity to tackle disease at the cellular level. Jim Datin, president and CEO of BioAgilytix, outlines a shift of investment into "the discovery and development of large molecule therapeutic proteins (as opposed to small, chemically manufactured active-substance molecules)". This, he states, allows companies to tackle conditions that were previously difficult to address, like oncology, neurology, and metabolic and infectious diseases.

Nowhere is the issue of last mile transportation more pronounced than in the processes that support clinical trials.

As biological products can be composed of sugars, proteins, nucleic acids, or live entities such as cells and tissues, guaranteeing the integrity of these time and temperature-sensitive products during transportation is a zero-tolerance business. To ensure patient well-being, investigational medicinal products (IMPs) need to be kept in temperature-controlled conditions of either 2–8°C or 15–25°C from the moment they leave the manufacturing site until they reach their final destination.

> "Guaranteeing the integrity of these time and temperature-sensitive products during transportation is a zero-tolerance business."

The packaging materials revolution

To date, the most forward-thinking temperature-control packaging providers have been keeping pace with change. Packaging materials such as vacuum insulation panels (VIPs) and phase change materials (PCMs) that freeze and thaw within the required temperature ranges for different pharmaceutical products, are combined to great effect in more advanced packaging systems.

Designed for longer transit times, these packages are robust and often guarantee autonomies of 96–120 hours. They are also reusable. This allows pharmaceutical companies to reach their own environmental benchmarks, as well as to meet the increasing demands for zero tolerance with respect to temperature excursions.

Softbox has been relentless in its commitment to technology and innovation, breathing new life – and new products – into temperature control packaging and logistics.

The effectiveness of high-performance shippers that often flirt with acute global climatic variations is well documented. But Softbox is now going the extra mile, leveraging some of this innovation to deliver a solution that is fashioned specifically for last mile transportation.

From depot to doorstep

Plans are already in place for hybrid transportation pods capable for protecting IMPs from depot to doorstep. The pods will comprise of an outer payload container that houses temperature-sensitive products, and if required, a smartbox to provide data to relevant parties in near-real time. IMPs will remain stable during the last uncontrollable critical miles to the patient's home.

> "Plans are already in place for hybrid transportation pods capable for protecting IMPs from depot to doorstep."

The pods will be easy to condition and completely reusable; at each appointment, patients can simply exchange a used pod with the investigator for a freshly conditioned one. The concept will allow them to take temperature-sensitive clinical trial medicines from the clinical investigator site to the fridge at home, safe in the knowledge that they will remain within their correct temperature range.

The brainchild is also a partial adaptation of the new Softbox Skypod, a thermally insulated packaging system designed to be carried by UAV/LTE-connected drones. It has completed trials successfully and is due to launch in early 2019. A global pharmaceutical company originally identified the need for a solution in the wake of devastating and life loss from Hurricane Maria in Puerto Rico in 2017.

The Skypod packaging includes a smartbox device powered by the internet of things (IoT) technology. It is geared towards tracking the package and transmitting data that can be viewed on a web and mobile app dashboard. This includes its location, near-real time external and internal box temperatures, as well as light exposure data (determined by the opening and closing of the lid) that signals any tampering during daylight. The dashboard app will flash alerts – whether on breaches of temperature ranges or defined geofencing parameters – to prompt appropriate action.

Skypod is the blueprint for CliniPod, the forthcoming clinical trial last mile shipper.

Breaking new boundaries

Softbox has been relentless in its commitment to technology and innovation, breathing new life – and new products – into temperature-control packaging and logistics.

By leveraging Skypod innovation, this latest clinical trial solution offers significant potential value to the pharmaceutical industry. Its importance cannot be overstated. With the amount of work and investment goes into all facets of the drug development and distribution processes, the idea of it all unravelling in the last mile is unthinkable.

Softbox is launching a superlative, temperature-control packaging system for new and existing temperature-sensitive IMPs. This is a giant step towards making the uncontrollable last mile controllable. ■

Further information
Softbox Systems
www.softboxsystems.com

Reusable, high-performance packaging to rent

Clinical trial temperature-controlled shipments are moving from single-use packaging shipments to reusable, high-performance packaging shipments in a rental model. **EMBALL'ISO** is a pioneer at developing reusable packaging and rental solutions, and, after a few years of implementation, its customers have received a significant return of experience.

New high-performance packaging has been developed in recent years with highly insulated material like vacuum-insulated panels (VIPs) and phase change material (PCM) cooling elements. This new insulated packaging avoids temperature excursion even on long shipments, mainly due to PCM's ability to go into hibernation mode when stored at specific temperatures. However, not all customers can move to these new packaging technologies due to the high cost involved. Those reusable packaging are five to ten times more expensive than single-use packaging.

A world leader in the design and manufacture of high-performance temperature-controlled packaging systems for the transport of pharmaceutical products, EMBALL'ISO's business model has shifted to offer high-performance isothermal packaging rental solutions over the last five years.

EMBALL'ISO's rental offer includes a rental fee for packaging and the option of a collection service managed by EMBALL'ISO at the final destination. Cleaning by UV treatment and quality control is also included in the service, as well as a follow-up on dedicated software. Additional services like ready-to-use or temperature data tracking can also be added. As soon as the packaging is shipped to the final destination (customer or subsidiary), the collection shipment is planned with the aim of offering the highest recovery rate.

Three main benefits

Among the benefits of this new model, the most prominent is the eradication of temperature excursion and therefore quality improvement due to the use of high-performance isothermal solution that they could not have afforded on a sales model.

The second main benefit is the cost reduction on every aspect:

- no more capital costs for packaging acquisition
- fewer or no more storage costs
- fewer conditioning costs due to the ease of use and conditioning of PCM.

The final benefit is the reduction of environmental costs due to the reuse of isothermal packaging. No waste management is needed and the entire isothermal solution – packaging and briquettes – is reused. This model is environmental-friendly, particularly over shorter travel times to the packages final destination, where it will be cleaned, quality checked and recorrugated. EMBALL'ISO's worldwide presence spans across four continents, with eight production sites in Brazil, China, France, Germany, India, Singapore, the UK and the US, and collection points in more than 80 countries. This global distribution helps customers to reuse isothermal packaging worldwide by shipping the isothermal solution back to its nearest factory. This model works for small packaging as well as for big pallet shipments in the reverse logistics model.

> "By working hand in hand with our customers, helping them and advising them on their rental management process, we manage to collect 98% of isothermal packaging on the selected shipping lane."
>
> **– Yann Martin**

Nevertheless, prior to implementing this rental, "you should be aware that you will have to define new processes with your logistic and production team, and it will definitely change your way of working together," says Yann Martin, global sales director of EMBALL'ISO. The communication with the isothermal packaging supplier and the final customer is crucial in order to maximise the return rate. "By working hand in hand with our customers, helping them and advising them on their rental management process, we manage to collect 98% of isothermal packaging on the selected shipping lane," Martin adds.

In a nutshell, pharma companies can drive their costs down and eradicate temperature excursions by renting high-performance reusable isothermal solution. Nevertheless, the human involvement to initiate this new process must always be taken into account. ■

Further information
EMBALL'ISO
www.emballiso.com

The ideal transport partner

AirBridgeCargo is the ideal partner for transporting temperature-sensitive products around the globe. From vaccines to laboratory equipment, the company's in-depth knowledge of the healthcare and pharmaceutical industry allows its customers to ship their products with confidence.

AirBridgeCargo's dedicated and qualified staff – including sales, customer services, operations and procurement – along with its state-of-the-art transport solutions, abc pharma active and abc pharma passive, allow the company to provide the quality handling procedures and control processes that are necessary for successful pharma transportation.

These special services are proof of AirBridgeCargo's commitment to deliver detailed and effective transportation options, particularly for those goods that require special attention.

There are many benefits to selecting AirBridgeCargo as a transport partner, including:

- skilled staff that are trained in handling healthcare products
- Boeing 747-8 and 747-400 aircraft that have three compartments that enable temperature settings ranging 4–29°C
- full compliance with IATA TCR and CEIV certification
- exact temperature monitoring from acceptance to delivery
- special packaging solutions and thermal blankets for palletised shipments
- customer service support, and online track and trace options
- tailor-made logistics solutions based on the customer's individual requirements.

abc pharma active is the solution for time and temperature-sensitive pharmaceutical products that need to be shipped in active containers. A variety of containers are used to keep healthcare goods as protected as possible, including dry-ice technologies. Shipped goods are kept at a constant temperature throughout the entire cargo journey, and the use of active containers mitigates risks for ambient temperature influence on healthcare products.

abc pharma passive is a solution for prepackaged pharmaceutical products. Within the required temperature ranges, and by the seasonal consideration of routes, healthcare goods are shipped efficiently and effectively. ■

Further information
AirBridgeCargo
pharma@airbridgecargo.com
www.airbridgecargo.com

Digitalization of Supply Chain Management

End-to-End Visibility Utilizing IoT

tss

Zero click: automation in the supply chain

Supply chain visibility is vital to the efficiency and data quality of clinical trials. Niclas Ohlsson, CEO of **TSS**, and Lars Nobert, corporate vice president of CMC clinical supplies at **Novo Nordisk**, discuss the collaboration project that has led to a digital and automated temperature monitoring solution.

The effective monitoring of temperature throughout the supply chain is of paramount importance in ensuring the safe and protocol-compliant conduct of a clinical trial. This is of particular concern in trials that incorporate insulin, which must be kept in cold storage and within specific temperature ranges when not in use to maintain its specifications.

Temperature deviations have significant impact. Each deviation causes the progress of the product along the supply chain to grind to a halt as checks are conducted to make sure it is still suitable to be dispensed. This process can last days or even weeks, potentially leading to failed patient visits. While investigations of the excursion are conducted, additional product is often shipped – but as approximately 70% of the deviations are found to be still safe to use, this can go to waste.

This issue is compounded when the product is in short supply. "We have trials which are Phase I, where you do the first human dose," explains Lars Nobert, corporate vice-president of CMC clinical supplies at diabetes-focused pharmaceutical company Novo Nordisk. "The product might be scarce, so there's not so much product to discard."

Productive partnership

Novo Nordisk has partnered with TSS, a provider of temperature monitoring solutions to the life sciences industry, to replace a paper-based system with the speed and efficiency of a digital approach. With all records online and immediately available, the new solution automatically responds to observations that the product is outside the intended temperature range. It supplants the manual process of deducting the time the product spent outside acceptable temperatures from the maximum time permitted at room temperature. "Prior to this it would take days to get this process and evaluate it, and now we're down to seconds," Nobert says. "So from a productivity, quality and delivery standpoint there's a huge gain and optimisation."

The new system works holistically to streamline the process of dealing with deviations. "It automatically aggregates all the information from the different parts of the supply chain into one universal truth," says Niclas Ohlsson, CEO of TSS. "It automates the notification and evaluation process so you remove all manual adding and analytics, and you get the right message to the right person at the right time."

The quality of data recorded by the digital system can also be used to drive refinement of the process. "We have a full view of the supply chain," Ohlsson says. "You can work on the fundamental parts that actually define the supply chain and improve it in terms of efficiency, cost and sustainability."

> "We designed the system with TSS, so we know for sure it will be easy to use, because we involved the people who are using it, both the site staff and our own staff."
> **– Lars Nobert**

Custom-made collaboration

The new temperature monitoring system is the result of close collaboration between TSS and Novo Nordisk. "We designed the system with TSS, so we know for sure it will be easy to use, because we involved the people who are using it, both the site staff and our own staff," Nobert explains. Ohlsson emphasizes the importance of beginning with a client's brief rather than fitting a ready-made solution to a problem. "You put the business problem first on the agenda," he says. "From that, you use your knowledge and your capabilities and skills to develop the innovative or adapting emerging technologies to solve or improve these business challenges or needs."

TSS is focused on innovation for the benefit of the healthcare industry. "When the internet came, and then smartphones, everybody talked about one click," Ohlsson says. "We're trying to move towards zero clicks, to automate as far as we can: simplification, automation and integration mean that user involvement is reduced and the quality of data is so much higher." ■

Further information
TSS & Novo Nordisk
www.tss.se
www.novonordisk.com

A sea change

The last 25 years have seen a dramatic evolution in clinical trials and processes. The delivery of investigational medicinal products to clinical sites and patients is continually shifting, yet the need to supply patients and sponsors with safe, flexible packaging remains. Kerry Taylor-Smith speaks to **Dr Wynand Smythe** about the challenges involved and how to maximise efficiencies.

For a large part of the 20th century, clinical trials were disorganised and fragmented, making it difficult to obtain a truly global representation of how a medicine could perform under regular conditions. The goal of any clinical trial is to support the marketing authorisation of new drugs globally, with trial findings going worldwide.

While such moves have increased the efficiency and speed of clinical drug development, they also present a whole new set of challenges to sponsors and pharmaceutical companies, including how to harmonise the process across the world in order to ensure that frameworks and requirements across all regions are met – adding another layer of operational complexity and expense to already costly trials. The process is complicated enough when running over several regions, because each area has its own detailed regulatory frameworks or ethical needs that might dictate approval and conduct of trials at a national level.

Regulators are therefore required to work together to synchronise requirements on a protocol-by-protocol basis, and regulatory and procedural requirements must be aligned to enable concurrent trial initiation across regions and introduce common processes to reduce operational intricacy. A delicate balance must be struck between maintaining the clinical trial's efficiency and satisfying regional regulatory requirements, while also adhering to good manufacturing practices (GMP).

Of course, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and the Clinical Trials Transformation Initiative (CTTI) has worked towards achieving this. Its aim has been to progress and drive the adoption of practices that will increase the value and efficacy of clinical trials. The CTTI in particular seeks to create a patient-centred system that is efficient and reliable, and allows timely access to evidence-based therapeutics prevention and treatment options.

More than meets the eye

How an investigational medicinal product (IMP) looks can be incredibly important in a clinical trial; after all, a pharmaceutical company or sponsor wants trial participants to see the test through from start to finish to see exactly how the drug performs and whether it has any side effects. Not only does the packaging have to be user-friendly – easy to open and labelled with clear, precise directions on how to take the medication – it must also display a professional appearance, while adhering to the rules and regulations governing medicines and clinical trials.

The packaging needs to be designed for function, keeping in mind the end user – specifically the trial participant. The IMP needs to be accessible, so it may be necessary to offer different

types of packaging to cater to a range of different users and their abilities; a blister pack or vial/bottle depending on the dexterity of the participant, for example. It is also important to choose the correct material for constructing the packaging: one with the ideal characteristics – for example, moisture permeability – to avoid adversely affecting the trial drug.

The global nature of today's clinical trials means that medicines are directed to multiple countries, each with their own requirements and regulations for packaging and labelling. Some regions within a country even have specific labelling requirements and wording, meaning that flexibility is needed in terms of what is printed on the label, as well as what that label is stuck to.

But it isn't just the bottle or blister pack that an IMP arrives in; how these are packaged, stored and transported is also significant. What if the medicine is temperature-sensitive, and could be destroyed by either too cold or too warm a temperature? Greater numbers of trials are using biopharmaceuticals, or advanced cellular and gene therapies, and in such cases the environmental conditions must be carefully and stringently controlled to preserve the IMP's efficacy. Variations in temperature during their storage, handling or distribution could not only affect the quality and efficacy of the product, but the data created for clinical trial evaluation, too – while at the same time presenting a substantial safety risk to the trial participant.

"Given that the primary aim of investigational drug intervention is to provide the right drug to the right participant at the right time, it's not surprising that drug shipment and delivery play a critical role in achieving this intention," explains Dr Wynand Smythe, Investigator for Lead Projects at the Clinical Research Centre at the University of Cape Town, South Africa. "At our research centre, the most noticeable changes in IMP packaging and shipment have been observed in the supply of cold chain products.

"Packaging material used to maintain cold chain has changed from the typical single-use frozen gel packs through to the reusable solid-plastic ice packs and currently to the new-generation phase-change materials," he continues.

Packaging has an increasingly important role to play in maintaining the temperature of shipments. It can vary from a passive and custom-designed container for a specific application to an active container able to heat or cool an IMP when necessary.

> "The global nature of today's clinical trials means that medicines are directed to multiple countries, each with their own requirements and regulations for packaging and labelling."

Products might also be shipped in different forms of packaging material, such as dry ice, liquid nitrogen or a phase-changing material, depending on what is most suitable.

"Similarly, temperature data-loggers accompanying the cold chain products have changed over time," explains Smythe. "Initially we received single-use loggers that required shipment back to the supplier to download and confirm IMP stability. Presently, we receive loggers that our site uses to download data and confirm IMP receipt and integrity with the supplier – for instance, when there is no need to ship the logger back to the supplier."

Get physical

Storage and transit temperature records are two of the many details that need to be maintained in order for suppliers to show adherence to the trial protocol, and ensure the credibility and truthfulness of data. The packaging of an IMP during shipment needs to maintain the integrity of an IMP prior to dispensing to participants, states Smythe, adding that typically, the primary, secondary and tertiary packaging maintain the "physical" integrity of the IMP, while ancillary packaging typically maintains the environmental conditions such as temperature and/or humidity of the IMP that it carries.

In order to maintain the stability of an IMP, Smythe believes the most logical solution to the problem would involve manufacturing a more stable IMP, not necessarily relying on packaging that protects its physical and environmental properties.

The increased globalisation of clinical trials, and the subsequent problems in distributing it worldwide, can cause delays in participants receiving medicines on time.

Global trade regulations can be a challenge as they can prevent movement of supplies between sites, delay deliveries and even unblind trial supplies. The problem could be the result of delays in customs-clearance processes, a lack of distribution capacity and poorly established distribution lanes.

"Notably, our site's greatest challenges in supplying participants with an IMP unexpectedly involve administrative challenges such as transit times through customs – for instance, on occasions an IMP may be held up at customs, resulting in it being exposed to conditions compromising its stability," says Smythe.

Smythe also notes, "the interactive web-response systems that some of our sponsors use to supply an IMP to our study site: the automated systems ensure that our site is resupplied with an IMP either when the IMP is dispensed [used] or about to expire". Such a system could ensure a suitably adequate supply of an IMP throughout the trial period.

But the work is by no means complete. Clinical trials, and how they are conducted, are still evolving, and the need for novel adaptive trial designs, platform trials and other forms of novel trial design continues.

Of the future, Smythe says: "I hope to see sustainable, reusable and lightweight cold-chain packaging used to maintain physical and environmental properties of the IMP during shipment. Similarly, I see 'stable' IMP manufacture neglecting the requirement for specialised shipment conditions." ■

Return of the pack

Pharmapack Europe will take place on 6–7 February 2019 at the Paris Expo, Porte de Versailles, France. The event will provide insights into the latest trends and innovations in the pharmaceutical packaging and drug delivery industries.

Network, innovate and learn with over 410 exhibitors and 5,290 attendees from more than 100 unique countries at Pharmapack Europe 2019. This year's event will deliver a two-day conference compiled of high-level industry expert speakers delivering discussions on current market trends in the pharmaceutical packaging industry along with an overview and analysis on regulatory changes in the EU and US markets.

This year will also feature a special Technical Symposium delivering a series of presentations from pharma leaders on tackling challenges with their new approaches coupled with case-study demonstrations.

The prestigious Pharmapack Awards will be returning for Pharmapack Europe 2019, celebrating the most innovative packaging and drug delivery solutions from the past year. The awards have two categories – the health product category and the exhibitor innovations category – and each are judged by a jury of independent industry experts and decision-makers. The awards will be presented on 6 February.

All exhibitor innovations submitted for the Pharmapack Awards will be showcased in the Innovation Gallery. Hour-long tours will also be available to guide visitors through the gallery and highlight the most innovative solutions.

The Start-up Hub will be returning for Pharmapack 2019. This programme is dedicated to young companies developing innovative technologies in the fields of pharmaceutical packaging and drug delivery, and will provide opportunities for them to showcase their products, network and pitch their companies to a panel of experts and an audience of industry professionals.

The complementary International Meetings programme will also be returning this year, which will allow exhibitors and visitors to prearrange meetings to network and share mutually-beneficial industry experience. ■

Further information
Pharmapack Europe
www.pharmapackeurope.com

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