September 2010

JOURNAL FOR CLINICAL STUDIES

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Respiratory Diseases in Children in Russia and Ukraine
Etiopathogenesis, Clinical Picture, Clinical Research and Legal Problems

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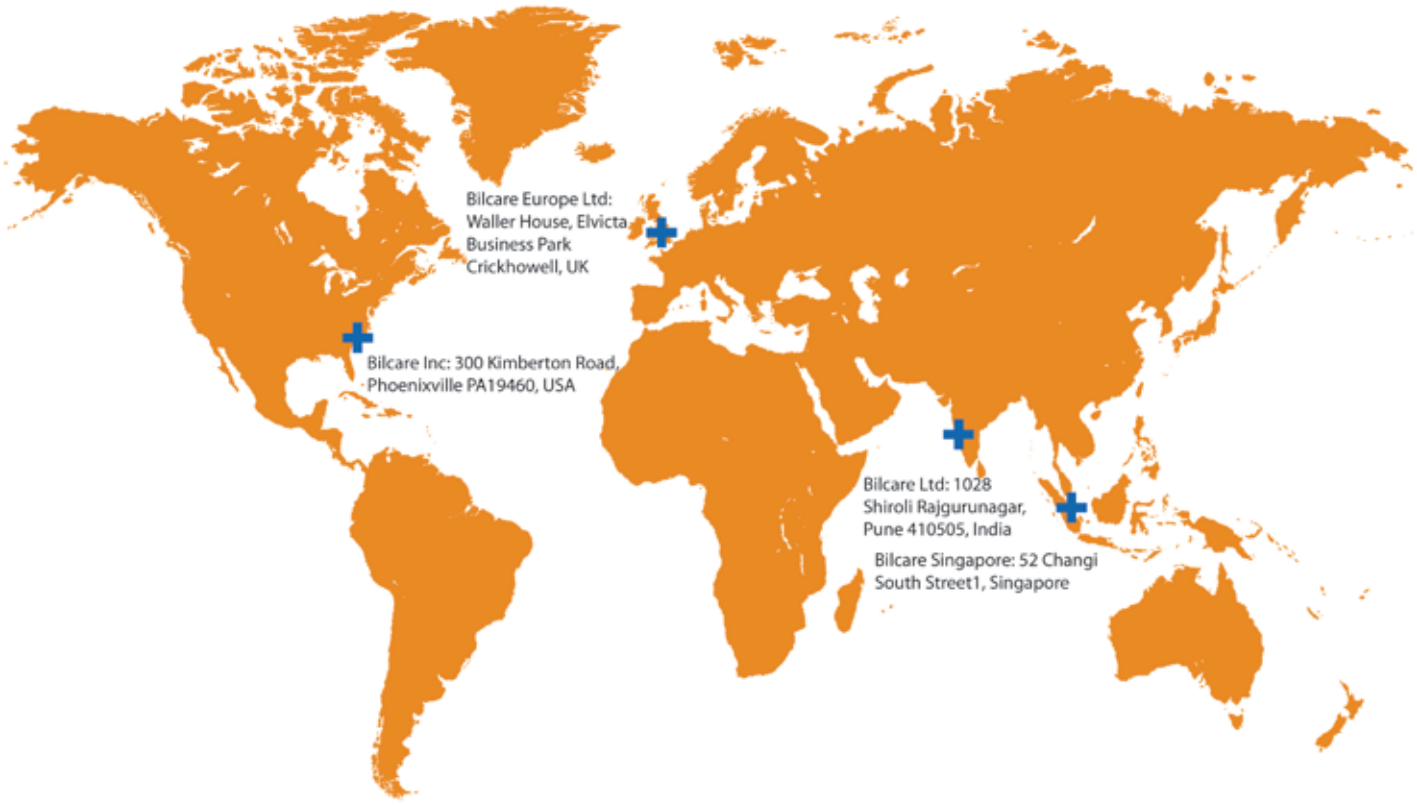

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Welcome to the 12th Issue of JCS.

It has been a pleasure and honour to work with so many respected members of the pharmaceutical and clinical research industry. We thank you all for the effort and support you have given to make JCS the most unique journal on its second anniversary.

We bring you again a wide range of relevant topics, which will guide you and give you a thorough insight into the progress made in the field of clinical research globally. Highlighted countries featured in this issue are — Australia, Pakistan and Morocco. Each of these countries have taken progressive steps to improve the environment for clinical research. For example, Trade Development Authority of Pakistan in collaboration with the Ministry of Health and Jinnah Postgraduate Medical Centre (JPMC) aims to invite the companies that conduct clinical trials to Pakistan and establish their centres in the country. In Morocco, clinical trials are now extremely organised due to the fact that most research ethics committees follow the guidelines of the Ministry of Public Health, which is compliant with ICH-GCP.

Our very popular Watch pages, where you get bite size, regular information on topics ranging from FDA & EMA guidelines, cardiovascular safety to clinical trial risk management and insurance, are a must read for professionals in this industry. We hope you can keep the issues for future reference.

Our therapeutic section covers chronic pain trials, therapies for the elderly and focus on the very important subject of paediatrics.

I take this opportunity to inform you about the Middle East & North Africa – Pharmaceutical Compliance Conference we are organising. I hope you can pencil the dates of 22 – 23rd of February 2011 in your diaries. The conference will bring together heads of regulatory affairs from FDAs in Saudi Arabia, Jordan, Egypt and Tunisia with leaders of global pharmaceutical and biotech companies to analyse and discuss the vital issues and opportunities in this fast expanding sector.

JCS has also launched its weekly newsletter. Clips of news concerning trials in emerging countries, up to date regulatory news, and relevant company information and links into various articles featured within JCS can be sent directly to you every week. Please visit www.jforcs.com and sign in.

I hope you enjoy the latest issue. We look forward to seeing you all at the 9th Annual Partnership in Clinical Trials in Vienna.

Mark A. Barker

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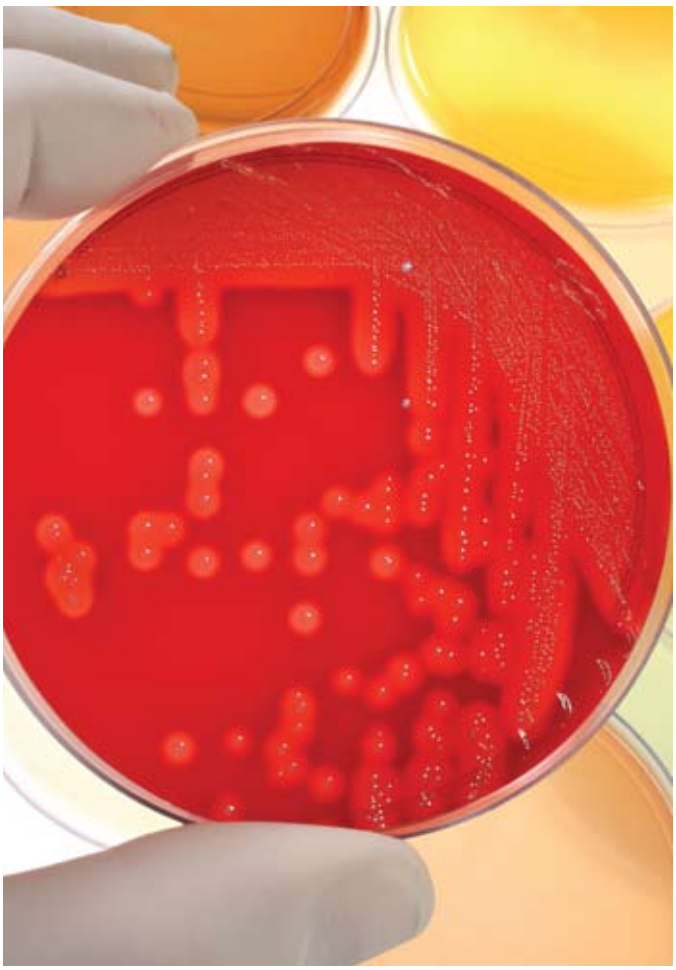
Informed Consent Elements

In December 2009, the Food and Drug Administration (FDA) announced in the Federal Register[1] the publication of a proposed rule to amend the informed consent regulations. The proposed change would require that the informed consent documents and processes for applicable drug, biologic, and device clinical investigations include a statement that clinical trial information for such clinical investigations has been or will be submitted to the National Institutes of Health/National Library of Medicine (NIH/NLM) for inclusion in the clinical trial registry databank[2].

Currently the informed consent document needs to include the following elements as per 21 CFR Part 50:

1 A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2 A description of any reasonably foreseeable risks or discomforts to the subject.
3 A description of any benefits to the subject or to others which may reasonably be expected from the research.
4 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5 A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.
6 For research involving more than minimal risk, an explanation regarding any compensation as well as an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7 An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research related injury to the subject.
8 A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the proposed rule becomes final, sponsors of clinical trials will need to include, in addition to the above elements, the following statement: "Information, that does not include personally identifiable information, concerning this clinical trial has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered clinical trials. This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain clinical trials to be submitted to the data bank."



It is FDA's opinion that knowledge of clinical trial information being included in the clinical trial registry data bank could affect an individual's decision to participate in a clinical trial.

Reference:
1. Federal Register: December 29, 2010 (Volume 77, Number 248) (Pages 68750-68756)
2. This data bank can be accessed at www.ClinicalTrials.gov

Alejandra Muntañola, RPh, MS, Project Manager, Thomson Reuters. Alejandra Muntañola graduated as a pharmacist from Complutense University, Madrid and further specialised in European Regulatory Affairs. She has worked for the pharmaceutical industry in Regulatory Affairs and is currently Editor Regulatory Intelligence for the IDRAC United States (US) Module at Thomson Reuters.
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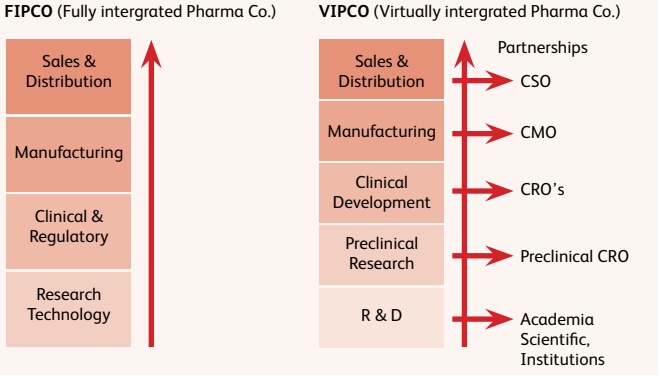
Collaboration Opportunities in Translational Research in Australasia

In May 2009, the Journal of Clinical Studies published a supplement called "Australia – Your Stepping Stone to Market". A number of articles were published that addressed the issues involved in Australia and New Zealand in undertaking preclinical studies, early phase clinical trials, the regulatory schemes available, as well as the rise of translational research and its challenges.

In terms of clinical trials, most of the early phase trials done in Australia are in fact for American and European pharmaceutical companies who repatriate the data for use in their regulatory jurisdictions since (when appropriately applied) Australia's and New Zealand's regulatory schemes facilitate starting early phase clinical trials rather quickly. This approach is now also increasingly deployed by Japanese pharmaceutical companies.

Australia and New Zealand have an excellent reputation in the field of medical research, and there is specialist expertise available in a wide range of areas associated with translational research, such as elucidating disease mechanisms, the role of genes and identification of biomarkers. These world class capabilities present in institutes across Australia and New Zealand provide the global biotechnology and pharmaceutical industry with the opportunity to establish new R&D business models which are characterised by an emphasis on long-term collaborations with the biomedical research institutes that have the right translational research expertise, facilities and technologies, which are difficult or costly to establish and maintain within a company.

Figure 1: The changing business model in the biopharmaceutical industry (from Biotech 2009: Life Sciences – Navigating the Sea Change, Burrill & Company).



To illustrate to the global pharmaceutical industry and academic researchers what is happening in the field of translational research, the 2010 Translational Research Excellence conference (TRX10) will be held in Brisbane, 11-13 October, 2010. The conference has the theme "Collaborate to Innovate" (www.trx10.com.au) and more than 100 speakers will present across three days in the fields of translational medicine, stem cell-based therapies, biomarkers, preclinical and clinical research, next generation sequencing and systems biology, funding of translational research, commercialisation, biologics/biosimilars/biobetters, and regulations.

Using modern technologies and computing power, the general aim is to link a patient's clinical data with data derived via the application of genomics, proteomics and systems biology, and ultimately enable personalised medicine, reduce healthcare costs and, for pharmaceutical companies, reduce R&D costs by early elimination of unsuitable therapeutic candidates. Several case studies were presented in the article by J. Barker and D. Gorse in the JCS (May 2009, 66-69).

Enriching clinical data with other types of patient data also brings about a more iterative approach to product development, i.e. drug development occurs in combination with treatment selection and (safety) biomarkers in the context of a solid understanding of disease pathology. However, there are many information management and organisational challenges in establishing a framework for obtaining, storing, managing and distributing patient-centric clinical and genomic/proteomic data. Not surprisingly, many new companies have been established over the last decade developing software solutions, informatics and statistics services for dealing with the vast amount of data generated.

Also, CROs are re-assessing their strategies in view of the need to provide translational research services to the pharmaceutical industry, and several CROs are now teaming up with biomedical research institutes. The demand for external services and specialised expertise by the biopharmaceutical industry is in areas like research in genomics and proteomics, screening and characterisation of (natural) product extracts and managing compound libraries, and preclinical research (bio-imaging, toxicity, molecular diagnostic tools, biomarkers).

Steve Burrill, founder and CEO of Burrill & Company refers to these developments as the change from Fully Integrated Pharma Co. (FIPCO) to Virtual Integrated Pharma Co. (VIPCO) as illustrated in figure 1. An interesting consequence of the move to VIPCO is the opportunity to introduce innovative financial arrangements that allow pharmaceutical companies to separate commitments in internal resources from financial investments, and operational control from asset rights.

All in all, there are many reasons to follow the developments in the translational research area closely, and to identify the new players, no matter where they are located, or whether they are an academic institute, CRO or biopharmaceutical company.

Otto Damsma. Prior to joining QCTN as business development manager, Otto Damsma held the positions of director of clinical data management and biostatistics and director of information management for a major international pharmaceutical company.
Email: otto.damsma@qctn.com.au

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Clinical Research from Morocco

It is a challenging task to write about the west when you are from the east, but the task can be facilitated using up-to-date technology and communication tools. What I previously knew about Morocco was its stunning nature and old universities, but what I have learned about Morocco is that it is a rich scientific environment that connects the west to the east. Nonetheless, the Moroccan government developed initiatives to facilitate the link between academic research and development in 1998, when they implemented a three-stage plan by creating incentives, building a research structure and directing research activities.

In Morocco, clinical trials are now extremely organised due to the fact that most research ethics committees follow the guidelines of the Ministry of Public Health, which is compliant with ICH-GCP. Research ethics committees are located mainly in faculties of medicine and in major hospitals around the country.

Moroccan clinical trials are usually multicentre studies, including European centres in France and Spain, US centres, and eastern centres in Tunisia, Egypt and Middle East. Clinical trials conducted in hospitals or institutions in Morocco require the approval of the National Ethics Committee in the Ministry of Public Health. Approval may also be required in some clinical sites from the local ethical committees found in those sites. Usually the documents required for submission to the local ethics committees in clinical sites are similar to those needed for approval from the National Ethics Committee in the Ministry of Public Health.

Any clinical trial in Morocco should comply with the governmental guidelines and laws that govern the procedures of conducting clinical trials. The National Ethics Committee Meets monthly, and the submission folder should contain: the standard request form or the application form; a letter from the medical director or clinical research organisation (if delegated) stating the main objective of the study; study documents (protocol, patient tools including diaries, questionnaires, informed consent form and draft case record form); investigator's brochure; investigators' / co-investigators' profiles; favourable opinion of investigator to participate in the clinical trial, if the investigational product is not commercialised in the country; description of lab exam; insurance of the trial, specifying the insurance for Morocco; letter indicating that treatment and para-clinic exams will be financed by the sponsor; letter indicating that adverse events will be the responsibility of the sponsor; clinical trial agreement; pre-clinical file of trial, and a fee of 10,000 Moroccan Dinar, the fees of EC to be submitted by cheque in the name of Association Marocaine pour la Bioéthique.

There are many clinical research institutes of excellence in Morocco, and most of them are university hospitals or military hospitals, including: Hop. D'enfant Avicennes, Rabat, Hopital Militaire, Hopital Militaire for clinical haematological services, Centre d'Oncologie Clinique Al Azhar and Centre d'Oncologie Clinique le Littoral. Phases of clinical trials that can be conducted in Morocco are Phase II, III and IV.

It is worth mentioning that five IRBs in morocco are registered with the US Office of Human Research Protection (OHRP). According to Clinicaltrial.gov, 51 registered studies are taking place in Morocco.

In conclusion, the Moroccan government is planning for a research-based academic environment. The Moroccan system is well organised for the take-off of multicentre research, and researchers are eager to show their capabilities of managing challenges.

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Cardiovascular Safety

The US Food and Drug Administration (FDA) has a range of advisory committees that review data from biopharmaceutical sponsors and provide recommendations on marketing decisions to the agency. These recommendations are non-binding, but the agency's decisions are typically in line with them. Advisory committees review data pertaining to the approval of investigational drugs for marketing, and postmarketing data when decisions concerning marketed drugs are called for. While examinations of postmarketing effectiveness data are certainly important, reviews of safety data often receive a higher profile.

On July 13th and 14th of this year the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held a joint meeting to consider data that some individuals felt indicated that a cardiovascular safety risk was associated with rosiglitazone, a thiazolidinedione drug for the treatment of Type 2 diabetes mellitus (T2DM). A similar meeting had been held on July 30th 2007, which focused on the cardiovascular ischemic and thrombotic risks of the thiazolidinediones (the other marketed drug in this class being pioglitazone), with a particular focus on rosiglitazone. A review of that meeting is instructive before discussing the key result from the recent meeting.

The 2007 meeting followed a publication in the New England Journal of Medicine that reported a meta-analysis odds ratio for myocardial infarction in the rosiglitazone group compared with the control group of 1.45 (95 % CI: 1.03-1.98, p=0.03). Since the lower limit of the confidence interval, 1.03, lies above unity, this numerical result provides purported evidence of a statistically greater incidence of myocardial infarction in the rosiglitazone group[1]. The appropriateness of the meta-analytical methodology employed in this report was widely questioned in the literature[2], but its high-profile publication led to the joint advisory committees' meeting.

At the meeting, rosiglitazone's sponsor and the FDA presented data before the committees' members. Such meetings are open to the public, and selected members of the public are invited to speak (typically for just a few minutes each). At the end of the meeting the committees' members vote on a predetermined set of questions, and are often asked by the committee chairperson to provide a rationale for their voting decisions.

On that occasion two votes were taken. First, the committees' members voted 20-3 that rosiglitazone increased the cardiac risk in patients with T2DM, although, as Krall[3] noted, "many members of the committee made statements accompanying their votes that drew a distinction between the risk as compared with placebo and the risk as compared with other antidiabetic drugs." Second, the members voted 22-1 that rosiglitazone should not be removed from the market. The FDA did not remove the drug from the market, although in November 2007 the sponsor agreed to add new warning language concerning potential increased risk of heart attacks to the drug's label.

The July 2010 meeting was similar in nature, but the list of predetermined questions to be voted upon was longer and more complex. Websites where the agenda, questions, and transcripts (day 1 and day 2) can be found are provided below[4-7], and readers are encouraged to read them: they provide a fascinating insight into the workings of these advisory committees. The key vote from present perspectives is this: 20 members voted against removing rosiglitazone from the market, and 12 members voted for removing it. Of the 20 members voting against marketing withdrawal, 10 voted for additional warnings and restrictions on use of the drug, and seven voted for additional warnings. At the time of writing this column, the FDA has not made any public statement on whether it will follow the committees' recommendations on this occasion.

Reference:

1. *Nissen SE, Wolski K, 2007, Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes, New England Journal of Medicine, 356:2457-2471.*
2. *Turner JR, Durham TA, 2009, Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance. Hoboken, NJ: John Wiley & Sons.*
3. *Krall R, 2007, Letter to the Editor, New England Journal of Medicine, 357:1776-1777.*
4. *www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM222622.pdf*
5. *www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM222625.pdf*
6. *www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM222628.pdf*
7. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM222629.pdf

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Technology to Manage Clinical Trial Risk and Insurance

Clinical trials represent up to 45 percent of the cost to bring a new product to market, and since patents are issued before a drug goes to trial, the faster that pharmaceutical and life science companies can bring their products to market, the longer they will enjoy sole distribution before competing against generic alternatives.

As clinical trials continue to grow in scope and complexity, so too does the regulatory environment in which they are conducted. Today, regulations and insurance requirements for clinical trials are becoming increasingly stringent, and vary from country to country. By leveraging technology and accelerating the sharing of vital clinical trials information, companies can win the critical "first to market" race.

Increased Globalisation, Increased Insurance

Over the past five years, the number of clinical trials worldwide has experienced double-digit growth. As companies move trials to other parts of the world, complex insurance requirements and risk management challenges also emerge. Missteps in the placement of insurance can delay or disrupt clinical trials, with every day lost translating into lost revenue.

The goal is to identify quickly what type of insurance coverage is required, when it will be needed, how much is needed, and to make the procurement as efficient and seamless as possible. Today, leading insurance brokerage firms have established a global network that can assist pharmaceutical companies not only with keeping pace with international clinical trial insurance requirements, but also offering technology to assist in the risk and insurance management process.

RMIS Solution: A Centralised Data Repository

Historically, companies used paper-based processes, emails and spreadsheets to monitor clinical trials and coordinate insurance coverage. However, this process can take several weeks, can be difficult to track and is open to human error.

A risk management information system (RMIS) enables pharmaceutical companies to create a centralised data repository, with all content available at the click of a button. As a result, the risk manager benefits from a 360-degree overview of their clinical trials insurance and risk, safe in the knowledge that it is up-to-date, auditable, clear and reliable.

Browser Advantage: Connectivity and Speed

A web-based RMIS fosters rapid connectivity among stakeholders across the globe and eliminates traditional silos of information among countries, insurance departments, research and development, safety, clinical research organisations, and other clinical trial professionals. Speed and accuracy are absolutely key in ensuring as little time as possible is spent gathering the necessary coverage to enable a clinical trial to start. With an online RMIS, this is immediately available.

Distributing Insurance Certificates **–** General, professional and product liability insurance coverage is often required prior to trial launch, as well as throughout the numerous phases of the clinical trial. At various stages, companies must distribute insurance certificates to the right regulatory agencies, which can be automated and tracked in an RMIS. At the same time, additional efficiencies are gained by virtually eliminating delays due to poor record management and planning.

Insurance Submissions and Renewals **–** An RMIS also assists risk managers in the insurance submission and renewal process. With underwriters now requiring more detailed and accurate clinical trial information, risk managers can leverage the RMIS to gather comprehensive information, leverage it in negotiations, and determine optimal optimal risk retention.

Data Tracking and Analysis **–** From the system, companies can run a broad array of clinical trial and risk management reports. The ability to run queries helps to create more transparency and accountability to external stakeholders and senior management.

Enterprise Risk Management **–** The information captured by the RMIS can be leveraged not only for the benefit of clinical trial management, but also for enterprise risk management (ERM). Clinical trial information can feed into a company's overall risk profile, so risk managers can formulate a strategy for optimal risk mitigation, retention and transfer.

Conclusion: Global competition is creating increased pressure on companies to make the development process more efficient and effective. By simplifying the issuance of clinical trial insurance certificates through technology, companies can bring new treatments to market more quickly, and can enjoy more time within their patent period.

An RMIS can reduce the time taken to gather all insurance cover from weeks to seconds, potentially resulting in millions of dollars in revenue. Rather than being a hurdle in the process (as was the case historically), the risk and insurance department can lead the way in the race to new efficiencies. With the world becoming ever more competitive, using RMIS technology as the baton to ensuring minimal time loss will make all the difference.

Kathy Burns, CEO of Aon eSolutions

Kathy Burns brings almost 20 years of experience in risk and insurance technology to her role as CEO of Aon eSolutions, the technology-solutions unit of Aon Corporation. Kathy was identified as a "Woman to Watch" by Business Insurance in 2006 and has been honoured with an Insurance Networking Leadership award. **Email: kathleen_m_burns@aon.com**

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Combination Products – the Road to Commercial Sales

A combination product is the broad term which has been given to define a single product consisting of two or more "active" entities and/or components designed to provide a therapeutic effect. Such products typically consist of a medical device and a pharmaceutical agent (drug), a medical device and biological agent, a pharmaceutical agent and biological agent, or any combination of all three entities. Individually, each of these entities has distinctly different approval requirements as imposed by law, regulations and directives.

While the practice of combining two products such as a medical device and a drug is not particularly new, the issues in so doing only came under scrutiny with regulators in the early 1990s, emerging into policies, procedures and regulations being imposed by the US Food and Drug Administration (US FDA). In grappling with this issue, the US FDA first looked internally within their organisation to determine how combination products should be handled and how responsibilities for the review and approval of combination products would be delegated within the agency (US FDA). What initially emerged were Memoranda of Understanding (MoU) between the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research. The essence of these MoU was, and remains, establishing the definition of which of these Centers would have the lead role as it relates to the review and approval of combination products. What is important to understand is the fact that the emerging policies, procedures and regulations developed by the US FDA have influenced other national health ministries to embrace very similar requirements as they relate to combination products, including those within the EU and Canada. However, unlike the US, the EU requirements are more complicated, in that sponsors of combination products remain confronted with the vagaries imposed by multiple states for combination products with drugs and/or biologics when combined with a medical device.

The ensuing regulations within the US define combination products as 1) a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; 2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; 3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product, where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or 4) any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product, where both are required to achieve the intended use, indication, or effect.

In considering the broad definition of a combination product, it is important to understand the practical effect for any given combination product and the strategic route to obtain approval to market the product. In real terms, the operative direction for meeting regulatory requirements, particularly within the US, will be dictated by which component of a combination product has the primary clinical therapeutic effect. Translating this means how the intended use and directions for use are defined. The US FDA, in designating and assigning which component of the agency shall have the primary responsibility and jurisdiction for premarket review, will first determine the primary mode of action of the product. If the primary mode of action is associated to a drug component, albeit associated with a device, the Center for Drug Evaluation and Research will have primary jurisdiction for review and approval and the Center for Devices and Radiological Health will act as a consultant. Likewise, if the primary mode of action is considered to be a biologic, the Center for Biologics Evaluation and Research shall have primary jurisdiction. While this may sound somewhat simple and straightforward, it becomes complicated by a number of factors, not the least of which can be influenced with the mindsets and experiences of the reviewers charged with making recommendations and decisions.

To complicate matters, both the sponsor of a combination product and the US FDA may have difficulty in clearly defining a primary mode of action. The US FDA, in its attempt to assign primary jurisdiction, has stated that where it is not possible to determine, with reasonable certainty, which one mode of action will provide a greater contribution than any other mode of action to the overall therapeutic effects, the agency will assign the combination product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole. When there are no other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole, the agency will assign the combination product to the agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product. Similarly, when a sponsor of a combination product has questions concerning the issue of primary mode of action, the US FDA has provided a mechanism whereby a sponsor can ask for what is called a 'request for determination'. This can be done informally or formally. In the case of an informal request for determination, the response from the US FDA may not be totally definitive so as to provide sufficient direction to a sponsor, and most certainly will not be binding upon the agency. In the

alternative, a formal request requires a clear and decisive response and is binding on both the agency and the sponsor. The good news in seeking advice or a decision from the US FDA as it concerns a combination product is that the agency has created a central contact in the Office of Combination Products. While this office provides direction and guidance, it is not the office or centre with jurisdiction for review and approval.

In real and practical terms under US regulations, if the primary mode of action for a combination product is associated with the drug component and the device is secondary, a sponsor will be required to provide for a New Drug Application and to also include elements for a Premarket Approval Application. Likewise with a biologic device combination where the primary mode of action is deemed to be associated with the biological component, a Biological License Application will be required which will need to include elements of a Premarket Approval Application. The underlying common factor, regardless of the component combination, is that clinical study data will be required in support of either application. As a precursor, a New Drug Application with an ensuing clinical trial will need to occur. The complicating issue which will confront a sponsor is how to construct and implement an acceptable, scientifically sound, clinical study. If both components in a single combination product, drug device or biologic device are already individually approved, designing a "new" clinical study should be significantly simplified compared with the situation where one or more of the components have yet to be approved for their intended use.

For many sponsors, particularly those who may be new in the venture of combination products, the process to achieve approval can be daunting. Without question it is time-consuming and costly. In many ways, navigating the requirements imposed under US regulations is useful to those seeking multinational approvals. Much of the detail and data that need be developed are essentially the same without consideration of borders. Providing the time and effort up front in the development of a sound strategic plan is essential and can help to avoid costly mistakes in having to start from the beginning. There are no shortcuts. The best advice is develop a plan, present it to the regulators and be prepared not only to justify your rationale and approach, but also to make certain that you listen to and understand the concerns which may be expressed. Important to this aspect is that you also need to be prepared to argue against impositions which may be deemed to be unreasonable or unfounded. However, it is important that any argument which may be fostered need be founded on clinical science as related to both safety and effective matters, not being contentious. The operative phrase is to choose your battles carefully for the sake of losing the war.

There is a wealth of information which is available on the subject of combination products from the US Food and Drug Administration web site. It would be highly advisable to pay a visit and become more familiar with the guidelines, policies, regulations and expectations on the subject of combination products. It is also advisable to determine the regulatory costs associated with providing the appropriate applications, since the US FDA has fee requirements associated with each type of submissions for approval.

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Clinical Research Dimension of Pakistan

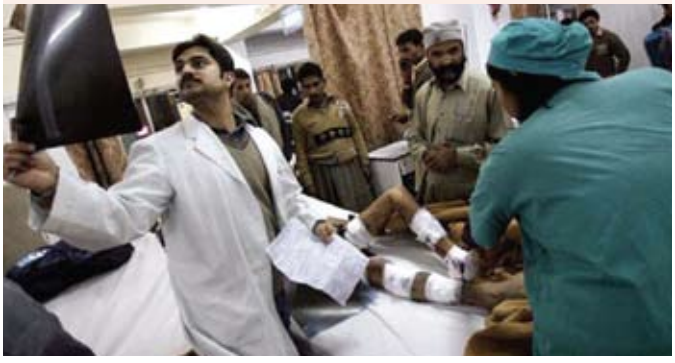
Pakistan is a Southeast Asian country which covers 796,095 km2 (307,374 sq mi)[1], approximately equalling the combined land areas of France and the United Kingdom, and the sixth most populous country, behind Brazil and ahead of Russia[2]. It is a gateway between South Asia, Central Asia and the Middle East; hence it is also termed the Gene pot of the world! Pakistan has a multicultural and multi-ethnic society, and host one of the largest young populations in the world. During the 1990s and early 2000s Pakistan was the second most urbanised nation in South Asia, with urban inhabitants making up 36% of its population[3].

Pakistan's Healthcare System

Pakistan has a population of over 170 million, and its healthcare system consists of facilities provided by government, private organisations and non-governmental organisations (NGOs), with 13,937 health facilities, 103,708 beds, 119,083 doctors and 9,590 dentists, trained in 148 medical schools and 21 dental schools. Among paramedics 69,313 nurses and 36,956 female health visitors are working in the healthcare sector. Three major cities - Karachi, Lahore and Faisalabad - comprise 82 % of the population. Most of the hospitals in the private sector have modern infrastructure and are equipped with modern facilities to provide healthcare, mostly by British- and US-trained physicians. In 2009-10 the government allocated Rs 28 billion for healthcare. The country has enjoyed an increase in life expectancy in the last two decades, with the average life expectancy for males and females being 63.51 and 67.77 years, respectively.

Clinical research was initiated by multinational pharmaceutical companies in the mid-1990s, followed by leading local companies. So far a number of Phase II, III and IV clinical trials and international observational studies / registries have been successfully conducted and duly audited by several local and international regulatory bodies. Phase I studies have also been approved by the Ministry of Health (MoH). Pakistan has emerged as one of the most attractive global venues for clinical trials, due to its geographic location, government support, literacy rate, urbanisation, availability of trained researchers and awareness of society.

Patient care at Dow University Hospital



The Clinical Trials Scenario

As the sixth most populated country in the world, Pakistan would appear to be highly attractive to pharmaceutical companies in their quest to involve more patients in their international clinical trials. As a former British colony, it has a medical teaching system which is mainly based on the British and American pattern. Furthermore, English is the medium of instruction and is often used as an official language, especially for medical record-keeping, and this would be of benefit to sponsors seeking to operate in the country. Operational cost-effectiveness would be high, due to the low value of the currency against the US dollar. For instance, trials for a standard drug in the US can cost up to $150 million, whereas a similar drug could be tested in Pakistan for less than half of that amount; this would also be an added attraction. Furthermore, Pakistan has a large pool of treatment-naïve diabetic, hypertensive and, particularly, cancer patients. The prevalence of diabetes is 12.14 % in males and 9.83 % in females; by 2020 Pakistan will have the fourth largest diabetic population in the world. It is estimated that over 50 percent of the population over the age of 50 is hypertensive. According to Globocan, more than 15,000 new cancer cases are reported annually, with the highest age-standardised rate for breast cancer in the world.

During the last two decades Pakistan has been involved in clinical trials with multinational drug companies like Novartis Vaccine Institute of Global Health, Abbott, GSK, Eli Lilly, Microport, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Otsuka and Bayer, followed by leading local pharma companies including Getz Pharma, PharmEvo and Ferozsons Laboratories; in various specialities such as oncology, neurology, psychiatry, endocrinology, cardiology, infectious diseases, women's health, vaccine and medical device studies etc. There are many renowned multinational CROs like Quintiles, Covance, Kendle, i3, Parexel, PRS Inc. etc. working either directly via sponsors or through their local collaborative partners/preferred vendors such as Dimension Research; consolidating their bases and expanding operations. The foundation stone of the CRO & Site Management Organisation (SMO) business was laid by a former Clinical Research Manager (CRM) of Eli Lilly Pakistan, Khurram Zaki Khan, in 2005.

Pakistani sites have participated in numerous pivotal Investigational New Drug (IND) studies and have achieved an extremely competitive enrolment rate, a high quality of data and compliance with ICH-GCP guidelines. In addition to Phase studies, Bioequivalance(BE), Bioavailability (BA), Pharmacokinetics (PK) and Pharmacodynamics (PD) studies and biomarker research are also being conducted in specialised centres at Karachi and Lahore. Validated/accredited laboratories are available in major cities. MoH Pakistan also encourages the expansion in the field of clinical research, and is now implementing the rule of local clinical data requirements for registration of new molecules in the country[4-5].

The MoH, academia and private institutions appreciate the

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benefits of clinical research to society, patients and institutes with regional and international collaboration. Most of the researchers and institutes are compliant with the ICH and Pakistan GCP to ensure the patients' protection and reliability of the data. Furthermore, to overcome the demand for trained personnel, certification courses and master programmes have been started for clinical research professionals at major postgraduate training institutes like Dow University of Health Sciences and AKU; these offer extensive insight into medical research to ensure competence and excellence in this field.

Approval / Authorisation Process

A comprehensive review system for clinical trials has been established by the Ministry of Health and the Pakistan Medical Research Council with participating hospitals. The clinical trial approval process is being supervised by the R&D department of MoH. The independent review board (IRB) or ethics committee of each participating institution has to review and approve the research protocols and relevant documents for subsequent approval by the MoH. Dossier requirements to the Ministry for approval are almost identical to those in the US, EU and UK, with no other pre-requisites except the translation of Informed Consent Form (ICF) into the national language. No separate permission is required for the export of biological materials outside Pakistan, once the protocol is approved by the authority. An import license is required if the drug is not registered or marketed; however for already registered products, MoH requires only IRB approval where the research is supposed to be conducted. The average timeline for approval by the MoH is 6-8 weeks, after the local institutional approval which also takes 6-8 weeks.

Drug registration in Pakistan currently takes place through the Drug Control Organization under the Drug Control Act of 1976; this body oversees areas such as R&D, pharmacovigilance and drug information. It also liaises and interacts with counterpart regulatory agencies and organisations in other countries, especially the Food and Drug Administration (FDA) for capacity building and exchange of information[5].

Future Prospects

Pakistan has a very vibrant pharma Industry. In 1947, there was hardly any pharma industry in the country. Today Pakistan has about 400 pharmaceutical manufacturing units, including those operated by 25 multinationals present in the country. The Pakistan Pharmaceutical Industry meets around 70% of the country's demand for finished medicine. The domestic pharma market, in terms of market share, is almost evenly divided between the nationals and the multinational corporations (MNCs). To date more than 1000 MNCs and local pharmaceutical companies operate in Pakistan, sharing a market of more than US$ 1.6 billion (IMS Q1 2010).

Key factors which could attract clinical trial business to Pakistan are the emerging awareness of benefits of clinical trials to all stakeholders, the increasing role of the private sector, the interest of pharma companies with the support of CROs, facilitating the participation in multinational collaboration with industry and academia. Another important factor is the establishment of new healthcare centres for disease-specific facilities supported by modern infrastructure, foreign-trained research physicians, pharmacists, statisticians and other study-trained personnel. Pakistan has proven that the capacity to recruit rapidly and inexpensively to evaluate larger groups of patients provides great value to its clients.

The Intellectual Property Organization of Pakistan (IPO) was established in 2005 and protects the rights of trademarks, patents, copyrights, genetic resources, and industrial and layout designs. IPO Pakistan empowers the Federal Investigation Authority and Pakistan Customs for intellectual Property Rights (IPR) violations. Patent rights relating to the pharmaceutical field are granted for new chemical products or new processes of an old product, formulation and composition, drug delivery systems and medical devices. Innovations (patents) and clinical trial data require submission for obtaining authorisation under separate articles of the Data Protection and Patent Protection acts. These developments will enhance opportunities for the clinical trials of bio-tech and medicinal products/devices. Legal protection of IPRs provides a conducive environment for substantial investment[5].

In Pakistan, the clinical research industry is at its launching pad; the homework is done, footings are strong, growth is encouraging, and Pakistan is learning rapidly from the experience of neighbouring countries. The challenge is to maintain the pace and get the focus of the R&D mega players; then the rest will be history!

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Advance Australia Fair?

A noticeable recent development in clinical trials has been sponsors increasingly conducting studies in emerging markets such as Latin America, India, Eastern Europe, Southeast Asia and China. These areas are of particular interest due to their large populations of treatment-naïve subjects and increasingly well-developed clinical development infrastructure, including medical and regulatory expertise and trained personnel. There is, however, one location that should not be overlooked – Australia. Long considered a highly sophisticated region, Australia is a potentially key geography as the industry strives to conduct high-quality and scalable global clinical research.

Going Global

In the past decade, clinical research has changed significantly. The days of blockbuster profits and sluggish development models have largely been replaced with more flexible and dynamic business models, industry consolidation through mergers and acquisitions and increasing cooperation among the main players. Developing in conjunction, and potentiating it in many ways, has been a move away from paper-based clinical development processes towards electronic, or eClinical, solutions, which enable enhanced data-driven decision-making.

Ten years ago the bulk of clinical research was carried out in the US, Western Europe and Japan. However, the need to cut costs, combined with access to treatment naïve-patients, willing investigators and the political dynamics associated with changes to the composition of the main global economies, have led to increasing globalisation of the clinical development process.

In recent years, new locations have emerged where clinical research is now routinely conducted with a high level of efficiency. Eastern Europe, India, China and increasingly Korea and Latin America each offer attractive levels of patient access and the opportunity to access quality medical care in the major conurbations. The importance of these locations is mirrored in the investments that major contract research organisations (CROs) are making in Latin America and APAC, specifically in countries such as Mexico, Argentina, Brazil, Chile, China, India and Korea, with locally-based clinical monitors, regulatory staff and other key personnel acting as a strong indicator of clinical research growth in these geographies.

Also included in the APAC region, Australia has emerged as a global clinical research destination, offering a unique blend of skills and flexible cultural alignment.

Heightened Clinical Activity

With a population of around 22 million, Australia has the 13th largest global economy. There are around 450 biotechnology companies and some 600 medical technology companies in the country, with over 100 life science companies listed on the ASX (Australian Stock Exchange), making Australia the leading location for biotech in the APAC region. The country's pharma organisations have also been attractive acquisition candidates. For example, the Danish company LEO Pharma acquired Peplin, and Cephalon acquired ARANA Therapeutics – each deal being worth more than $300 million.

Global CROs such as Kendle, Covance and Quintiles have all made their presence felt in the country in order to serve the needs of global pharma as well as the emerging biotech sector in the local market. Local CROs offering special skills and expertise have also made their mark. Novotech Pty, the largest of Australia's CROs, with operations in India, South Korea, Malaysia and Thailand in addition to Australia and New Zealand, offers Australian businesses a local relationship, but has also positioned itself as a local partner for CROs in other regions, ideal for sponsors who prefer a network of locally-based CROs in a variety of regions instead of a global CRO for large projects. Novotech also offers full clinical services designed for the sponsor that lacks a presence on the ground in the APAC region.

Alek Safarian, CEO of Novotech Pty, notes, "Australia makes a great headquarters from which we can build a dynamic and competitive CRO platform across APAC based on access to world-class medical facilities and a tight and effective regulatory environment."

As well as having representation from most of global pharma, the country also boasts some significant local businesses. Chief among these is CSL, headquartered in Melbourne, Victoria, which ranked as the 31st largest organisation in PharmExec's 2010 report on the world's top 50 pharmaceutical companies. CSL is a truly global business with affiliates in the US and Germany, and was among the very first to conduct successful clinical trials on a vaccine for H1N1 in 2009.

Dr Russell Basser, SVP Global Clinical Research and Development at CSL Ltd, states, "High-quality medical training and internationally competitive biomedical research institutes in Australia, and the attractiveness of the country to incomers, means we have access to great quality clinical and translational science researchers. CSL certainly sees Australia as a vital part of our ongoing R&D efforts, reflected in the recent announcement of plans to build Australia's first large-scale biotechnology facility for the late stage production of new recombinant therapies for a variety of disorders at our manufacturing site in Broadmeadows."

Benefits of being Down Under

There is no doubt that Australia can provide the highest quality clinical research and medical care. Organisations such as the Royal Melbourne Hospital and the Victor Chang Cardiac Research Institute have an academic and professional standing equal to any US or European institution. Australia offers access to highly trained medical, clinical support, co-ordination and regulatory personnel who are very familiar with ICH/GCP standards, as well as a highly skilled research community with a long tradition of researchers assuming expatriate research positions or further study secondments involving Australian institu-

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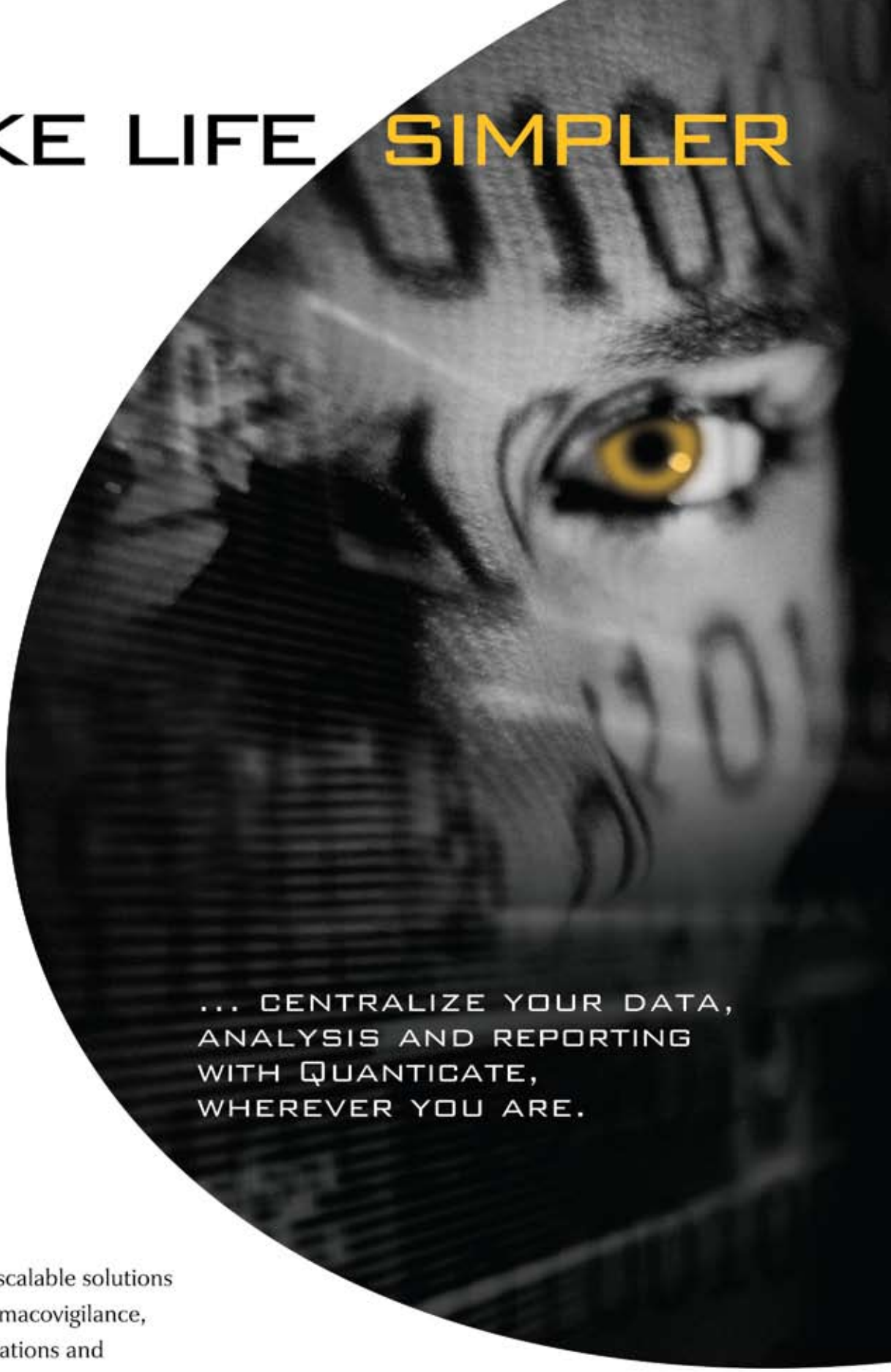

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tions and counterparts in the US and UK.

With a largely Western-based mindset, Australia benefits from a history of running US Food and Drug Administration (FDA) and European Medicines Agency (EMA) registration studies in the APAC region, and most of the major Western-oriented CROs have locations in the country. With English as the lingua franca of the global pharma industry and so many of the main pharma businesses located in the US, Australia's unique language and cultural alignment must not be underestimated.

In addition to its Western influences, Australia is indeed a part of a greater APAC/ASEAN region, with increasing Asian influence, and so represents a gateway to greater clinical trial involvement in the area. Its unique geographical location often turns the challenges of running trials into opportunities. For example, the ethnically diverse Australian population includes a significant sub-population of Japanese patients, meaning Australian sites can be factored into global trial sequences. The country's location in the southern hemisphere also offers a major benefit in that seasonal studies, such as for flu or allergy therapies, may be conducted at a time when the rest of the traditional clinical research locations are in the opposite season.

Besides offering excellent local medical and research facilities and acting as a geographical and cultural gateway to APAC, a key factor in the success of running trials within Australia has been the country's ability to conduct complete Phase I studies within a single country, which is certainly a competitive advantage especially as its relatively small population does not limit recruitment.

Australia's Therapeutic Goods Administration (TGA) is responsible for regulatory approvals regarding early phase trials. As first-in-man (FIM) study protocols do not apply to approved products, they fall under either the Clinical Trial Exemption (CTX) scheme or the Clinical Trial Notification (CTN) scheme. Most early phase studies go through the CTX scheme and require TGA review.

After Phase I – the Challenges Ahead

The successful environment for Phase I studies does not always, however, effectively translate to Phase II and beyond, and this points towards some of the challenges that Australia faces if the country wishes to build on its unique combination of geographical, cultural and medical advantages.

Australia is a federation of states with each state exercising its local power, resulting in the lack of a harmonised approval process for clinical programmes operating across multiple states. At a national level, it is hard to see who actually "owns" the clinical trial process in the same way that the FDA "owns" the process in the US. Although regulations sit largely within a governmental group known as the Department of Innovation Industry Science and Research, there are many additional interconnected players in Australia's pharma industry, such as the NHMRC, ADEC, HOMER, TGAAHMAR, state governments, individual hospital institutions and health departments, and industry groups such as AusBiotech, PIC (Pharmaceuticals Industry Council) and ARCS Australia Ltd (previously the Association of Regulatory and Clinical Scientists). Some progress is being made in the post-Phase I regulatory area with, for example, the state of Victoria leading the charge towards a harmonised "pre-approved" Clinical Trial Agreement (CTA), however, inter-state rivalry compromises must be made. Australia's states need to legislate in order to recognise and accommodate the federal harmonisation initiative.

Australia's organisational complexity, coupled with its relatively small and ethnically diverse population, limits the extent of the country's participation in global studies. Moreover, the fact that whilst costs are lower than in the US and European Union (typically by about 15-25 %), they are still higher than in Asian countries in the region. With its major economic interests resting on the extraction (mining) and agricultural industries, it has taken some time for the government to recognise the importance of the development and organisation of Australia's clinical research industry.

Australia Fair Does Advance

Australia is a country with excellent technical and medical infrastructure, as well as a prime geographic location, with close cultural ties to huge emerging markets in APAC as well as to the major sponsor organisations in the US and Europe. However, the country is facing challenges largely of its own making. It is imperative that Australia's government and clinical research industry work together to recognise the importance of a healthy and competitive clinical development sector, and implement the educational and institutional reforms needed to ensure that indeed, Australia fair does advance.

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Eastern Influences on Patient Recruitment: *Focus on: Asia*

PEER REVIEWED

As the world's largest continent, comprising 44 countries and 4 billion people, Asia is replete with possibility in the clinical research realm. Recent data, available at Clinical Trials.gov, show 5681 trials actively recruiting participants in the North, South, Southeast and Eastern quadrants of the continent. Of particular note, a hotbed of clinical activity is underway in China - a standout economy among the BRIC (Brazil, Russia, India, and China), four countries on similarly accelerated paths of economic development (Figure 1).

China's double-digit annual growth rate in research and development surpasses expansion in established markets such as the United States, the United Kingdom and Japan. According to the 2010 Global R&D Funding Forecast, the country outspent Japan in R&D this year, and is expected to match aggressive spending in Europe in 2018 and rival US R&D spending in 2022. This phenomenon is fuelled by several factors, including establishment of clinical trial laws (Figure 2), alliance with the World Trade Organization, and formation of the State Food and Drug Administration in 2003. But with progress comes new challenges, namely increased competition, cost concerns and trial delays.

Increased competition seems largely the result of continued industry consolidation - a consequence of last year's global recession, which decreased the number of biotech companies and reduced R&D funds. Further eroding industry investments are declining numbers of new products in the pipeline and increasing numbers of generic drugs. The pharmaceutical market experienced a 2 percent decline in 2009, representing the first decrease in 50 years. Projections through 2011 only anticipate a 2.2 percent annual growth rate.

Despite general downturns, the Asian markets remain resilient, offering many potential advantages from a patient recruitment perspective, including access to a larger number of treatment-naive patients. A.T. Kearney, a global management consultant firm, conducted an analysis in 2009 highlighting preferred global destinations for clinical research. Among the 16 countries making the cut, five were in Asia, including the number one-ranked China (Figure 3).

In addition to abundant patient pools, strengthening regulations and research-minded physicians, cost efficiency is a major incentive for conducting clinical trials in Asia. For example, according to some estimates, per-patient costs for clinical trials in India are approximately 40 to 60 % of costs in North America and Europe.

Asia's clinical potential was just capturing international attention four years ago when the author led a delegation of 10 clinical research professionals to China to forge relations and exchange ideas for advancing the clinical trials industry. The visit was part of the Ambassador programme based in Washington, D.C., and founded by former US President Dwight Eisenhower. Its mission is to help individuals gain a better understanding of global cultures through firsthand travel experiences. Over the course of 13 days, the delegation toured four cities and met with pharmaceutical companies, hospitals, site management organisations, a pharmaceutical manufacturing plant, and a contract research organisation. Interactions included in-depth discussions about good clinical practice, informed consent and patient recruitment techniques.

What the group learned then, and what remains true today, is that developing tactics to overcome clinical trial challenges is insufficient; you also need a comprehensive strategy for applying them. To that end, the author recently led a two-day training session on "Effective Clinical Site Management & Pa-

Figure 1: BRIC Briefs

Brazil
Touted as the gateway to Latin America, Brazil's strength as a clinical research centre lies in numbers: a large treatment-naïve population of 201 million people, 8000 hospitals, 96 medical schools and 415 institutional review boards. While those figures are impressive for a developing country, perhaps the most important calculation is Brazil's pharmaceutical market index - a 14.5 % compound annual growth rate forecast through 2014. The country has rather sophisticated guidelines governing the conduct of clinical trials, as detailed in "Rules on Research on Human Subjects" (Resolution CNS 196/96 – "Normas Para Pesquisa Envolvendo Seres Humanos").

Russia
Russian study volunteers are generally very compliant in terms of keeping appointments, taking study meds, recording in patient diaries, and rarely withdrawing consent. They also seem to be highly motivated to participate in studies to gain access to the best facilities and the best physicians at no cost. Their high level of compliance may be because, in Russia, doctors continue to be seen as influential authority figures, and patients value their opinions. Some research suggests that, on average, study subjects tend to be fairly well-educated.

India
India was formerly overlooked by pharma companies because of limited intellectual property protection and the preponderance of generic pharmaceuticals produced by indigenous companies. Trial ethics also came into question following a survey by the former US National Bioethics Advisory Commission, which revealed that 25 percent of clinical trials conducted in developing countries did not undergo ethical review. Today, patent protection is no longer a barrier, as India now complies with Trade-Related Aspects of Intellectual Property Rights. Additionally, the Academy for Clinical Excellence and Institute of Clinical Research have been established to educate doctors in ICH-GCP guidelines and ethical trial requirements.

China
Clinical research in China is very much an emerging enterprise. With a population of 1.3 billion, much of it treatment-naïve, the country is a highly anticipated venue for clinical trials. See article for additional details.

Figure 2: China's Clinical Trial Laws and Regulations

- Drug Administration Law of the People's Republic of China – effective Dec. 1, 2001
- Regulations for Implementation of the Drug Administration of the People's Republic of China – effective Sept. 15, 2002
- Regulations for the Supervision and Administration of Medical Devices – effective April 1, 2000
- Chinese GCP Guidelines updated in 2003

tient Recruitment" on September 2-3 in Singapore. This focused on: 1) understanding the importance of good site selection to assist in the navigation of the clinical trial project; 2) developing a strong working relationship to ensure proper conduct of the trial in accordance with applicable laws and regulations; 3) building and maintaining a successful budget through contract and finance monitoring; 4) achieving an international standard multi-centred clinical site; and 5) designing an advanced patient recruitment and retention plan for a seamless clinical trial.

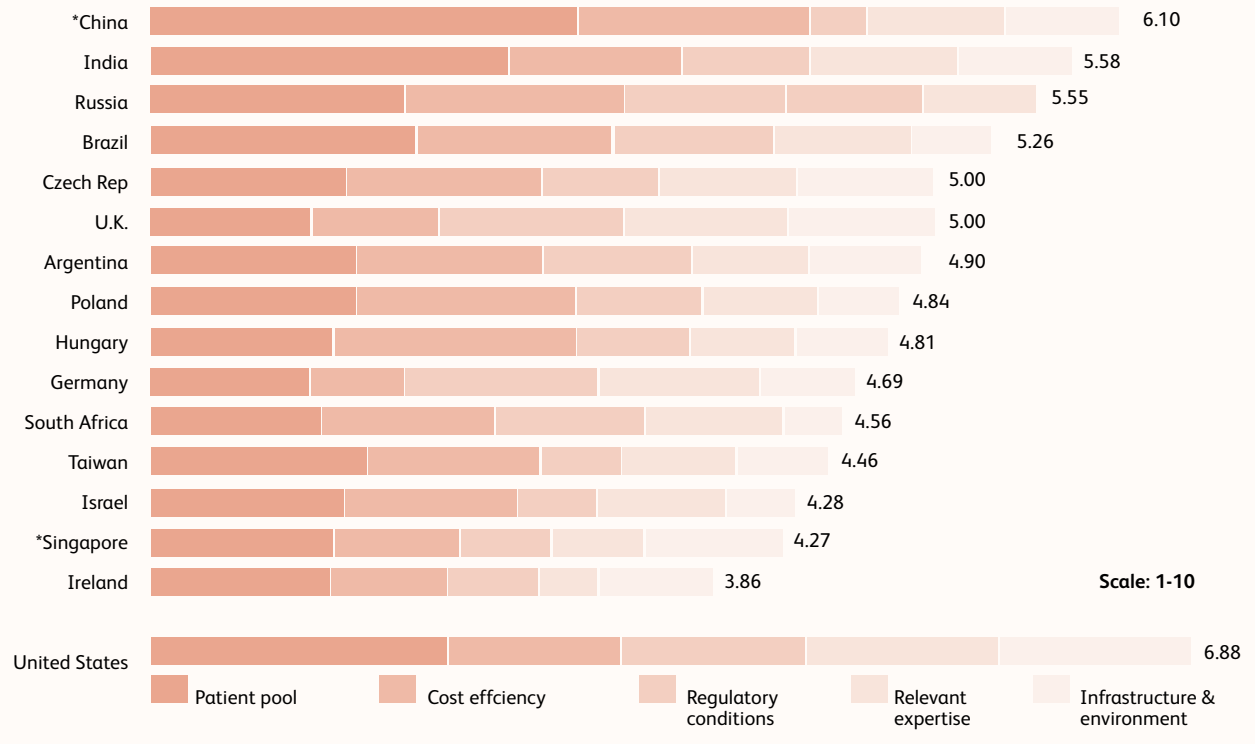
A DAC survey of 25 session attendees, all of whom work and reside in Asia, revealed that while the region has many positive attributes for conducting clinical trials, lack of awareness coupled with trial delays hinder the process. With respect to delays, attendees pointed to ethics committee approval times, competing studies and investigator selection. Reported EC approval times ranged widely from two weeks to three months, but perhaps the most significant delays occur before enrollment even gets underway. A case in point: in China it can take nine to 12 months to obtain approval from the State Food and Drug Administration (SFDA) to conduct a trial. Add to that the time required to evaluate and initiate sites, obtain drug import licenses, and recruit patients, and the delays can seem insurmountable (Figures 4 and 5).

Variances in Recruitment Regulations

The regulatory and ethical climates relating to recruitment practices differ regionally, and dissecting the guidelines can be difficult. The need for recruitment support in Asia depends on how recruitment is defined. When viewed from the standpoint of strict direct-to-patient study awareness strategies, external patient recruitment initiatives may be less relevant or appropriate in densely populated areas with specialised healthcare institutions, than in other areas where patient access is more restrictive due to geographic spread, or competing trials. For these regions, tools and materials developed to facilitate patient identification within individual institutions are more appropriate than public awareness-building campaigns.

Based on extensive research and practical experience supporting patient recruitment in 66 countries, DAC has found that patient recruitment is rarely mentioned in government regulations. When included, most of the guidelines discuss recruitment methods in the context of requiring ethics committee review, but rarely explicitly address whether certain strategies are allowed or prohibited. For many countries, recruitment methods are deemed permissible as long as an ethics committee approves the proposed methods. Many recruitment strategies commonly used in the United States are seldom employed globally, based more on tradition than regulatory restrictions per se. Regulations will broaden to support activities

Figure 3: Overall Country Attractiveness Index: India Second Most Preferred Destination *Source: A.T. Kearney, 2009*



as more clinical trials are conducted in Asia. As regulations are refined and geographical borders blend, the region is awakening to traditionally Western methods of reaching subjects, including call centres, website marketing and social networking, among other tools (See Figure 6).

Recruitment challenges aside, another confounding aspect of clinical trial management in Asian culture is patient retention, according to Theshinee Chuenyan, RN, head of clinical and office operations at IATEC - a CRO based in Bangkok, Thailand. Chuenyan suggests the paternalistic relationship between patients and doctors facilitates compliance with trial participation; whereas inadequate follow-up contributes to attrition.

"Getting patients to participate in a clinical trial is not as much of a problem because it is customary in Asian culture for patients to comply with their doctor's requests," she said. "Not enough emphasis is placed on informed consent; therefore, patients are inadequately educated about the process of clinical trial participation. Also lacking are educational materials and communication to keep patients engaged until the trial ends. Over time they simply drop out."

DAC's survey respondents echoed these sentiments, noting patients' general lack of awareness about their rights, and underscoring the importance of the doctor-patient relationship in averting attrition.

Using strategies reminiscent of the now-obsolete Western tradition of "making house calls", Chuenyan and her colleagues maintained less than 5 percent attrition in an HIV clinical research trial in Cambodia by dispatching nurses to villages to check on study participants, answer questions and provide personalised care. While such tactics are likely time- and cost-prohibitive for most clinicians, they should serve as a guide for going the full distance to retain trial participants.

Developing effective and informative patient education materials is a must in the clinical trials industry. Nowhere is this more important than in the informed consent document. One of the primary principles regarding informed consent is that "the information that is given to the subject or the representative shall be in language understandable to the subject or the representative."[1] Due to the highly technical nature of investigational research, presenting complex information in the simplest form can be challenging.

In general, health-related information is more difficult to comprehend than most other types of information. In the United States, per Food and Drug Administration (FDA) regulations, the Institutional Review Board (IRB) ensures that technical and scientific terms are adequately explained and that the informed consent document properly translates complex concepts into simple language that the "typical" subject can read and comprehend. Most IRBs stipulate reading levels for such documents as part of their responsibility to ensure that research subjects understand the informed consent. Similarly, ethics committees may require that the consent form be written below a specific grade level to more appropriately reflect the reading levels within the community from which prospective subjects will be recruited. While regulations directly address requirements for the informed consent document, these principles apply to any type of patient educational materials.

Written informed consent forms are gradually being promoted and implemented in Asia to meet the requirements of good clinical practice (GCP). Prior to the issue of GCP in 1999, many people were unfamiliar with the clinical trial as an emerging area. Asian people conventionally regarded the signature as something similar to a self-selling indenture. As a result, many subjects still orally agree to cooperate in trials, but refuse to sign their names on the written document.

To mitigate these issues, measures are being taken in Asia to protect trial subjects, including establishing GCP training centres for clinical trial investigators, doctors, pharmacists

Figure 4: Enrollment delays: distribution of delays in site enrollmentfor patient recruitment

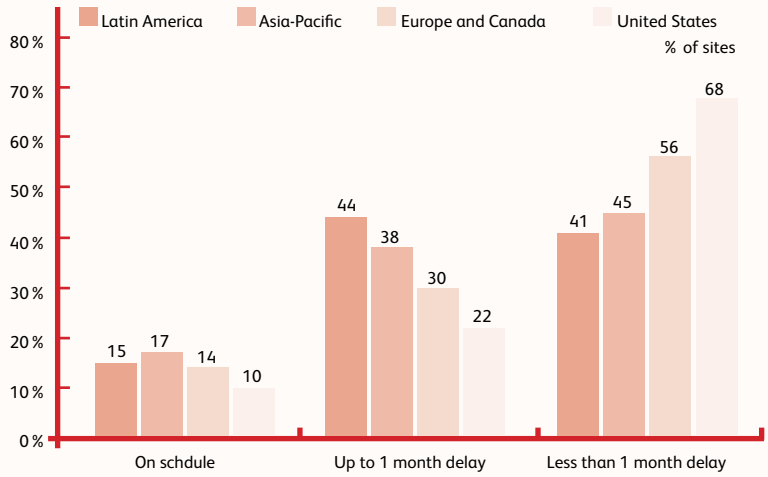


Figure 5: Regulatory Environment for Asia Pacific

Country	Current SSV-SIV times (Ave days)	Comments
Singapore	203	Amended insurance coverage regulation
Malaysia	217	1. Products of bovine/porcine origin to be listed ICF as well as labels 2. Imports from Israel banned
Philippines	200	New requirement for withholding tax delaying CTA execution
Taiwan	270	Challenging CTA negotiations – Q template heavily recommended
Korea	215	Lab kit import license now required
Thailand	210	MOPH site taking longer for EC approval
Vietnam	245	
Indonesia	267	Review on export of biological samples expected soon
Hong Kong	206	Drug sample (dummy) required for RA submission
India	265	License required from DGFT to export blood samples (+2 weeks)

Figure 6: Global Recruitment Strategy Deployment

Country	Utilization
United States	A+
United Kingdom	A
Australia	A
Germany	A
New Zealand	A
Spain	A
Puerto Rico	A
Italy	A
Ireland	A
Israel	A
Mexico	A
Canada	A
Switzerland	A
Japan	A
Belgium	B
Brazil	B
France	B
Netherlands	B
Poland	B
India	B
Tunisia	B
Argentina	B

Country	Utilization
Austria	B
Chile	B
China	B
Colombia	B
Costa Rica	B
Croatia	B
Czech Republic	B
Guatemala	B
Hong Kong	B
Hungary	B
Indonesia	B
Korea	B
Panama	B
Peru	B
Philippines	B
Portugal	B
Romania	B
Russia	B
Serbia	B
Singapore	B
Slovakia	B
Slovenia	B

Country	Utilization
South Africa	B
Taiwan	B
Thailand	B
Turkey	B
Ukraine	B
United Arab Emirates	B
Venezuela	B
Belarus	C
Bulgaria	C
Denmark	C
Egypt	C
Estonia	C
Lativia	C
Lebanon	C
Lithuania	C
Malaysia	C
Morocco	C
Kazakhstan	D
Finland	E
Norway	E
Sweden	E
Greece	F

Ranking scale: **A+** 100 % **A** 75-100 % **B** 50-75 % **C** 50 % **D** 25-50 % **E** 0-50 %

and sponsors; setting up a system to periodically evaluate clinical trial bases; and protecting subjects' benefits and rights by legal means.

Such progress is encouraging. Despite the preponderance of treatment-naïve patients and other attributes, clinicians in Asia are under no illusion that meeting enrollment goals is a sure thing. There remains a high unmet need for targeted patient recruitment and retention strategies, as well as continued education on ethics and law. Astuteness in regulatory requirements is but one prerequisite for implementing an effective recruitment and retention programme in Asia. A number of variables contribute to success. Among these are the establishment of rapport, trust and mutual commitment to study goals among research sites, the CRO and the sponsor. From these relationships arises enthusiasm among sites to embrace and execute recruitment strategies. Taking the time to invest in relationships may be the best recruitment strategy of all. Beyond their oversight, institutional policies and physician attitudes can heavily influence recruitment and retention practices. The lines of communication must remain open to ensure strategies are understood and fully executed. In doing so, sites will be better equipped to manage challenges as they arise, and employ methods to avoid study delays.

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Innovative Designs for Chronic Pain Trials

PEER REVIEWED

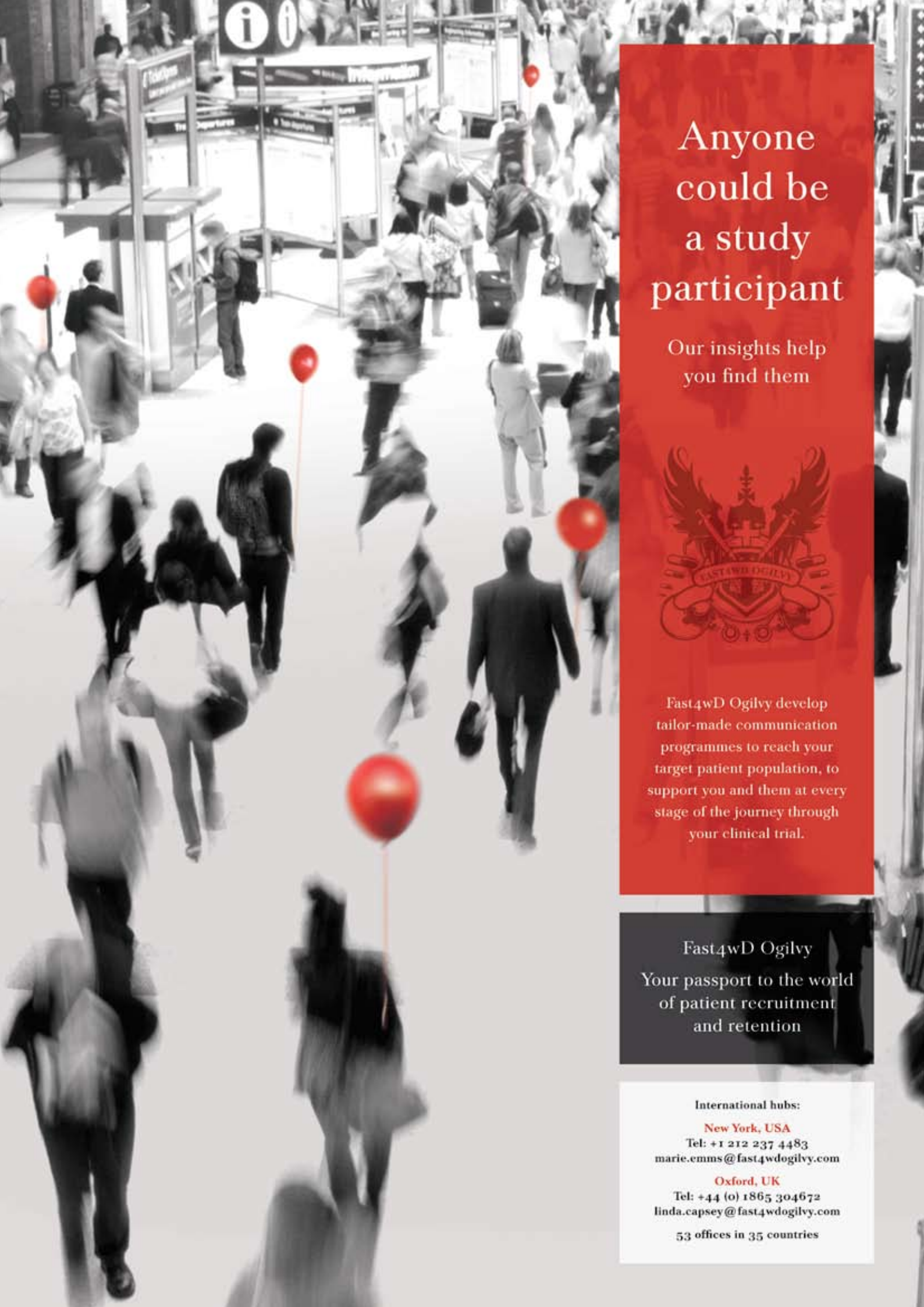
Despite a plethora of information gathered across the fields of neuroimaging, genetics/genomics, proteomics, and neurobiology that has enhanced our basic knowledge of the mechanisms mediating the perception of pain, there has been a relative dearth of approved novel treatments for chronic pain[1]. Simply stated, the advances in discovery research have not reliably translated into more effective, affordable, and safer pharmaceutical products, and it is unclear if the major reason for this lack of approved compounds, in spite of a general increase in the number of clinical studies, stems from a genuine lack of compound efficacy or from an inability to detect a positive signal in truly efficacious compounds. This review highlights innovative trials designs that may improve signal detection for novel therapeutics in chronic pain with a predominantly proof of concept emphasis.

It appears that our understanding of the basic sciences in analgesia has outstripped our ability to adequately assess treatment efficacy in an appropriately designed experiential setting. This sentiment is evidenced by the recent increase in "failed" trials, and not just "negative" trials, in which approved active comparators fail to separate from placebo, suggesting that our ability to dissociate signal from noise has been compromised. There are numerous reasons for a lack of assay sensitivity, but one of the biggest culprits appears to be an increase in placebo response – which seems to be steadily growing over the past decade. Much like the clinical trials in depression and anxiety that have long been plagued by an increasing placebo response, recent interventional studies in chronic pain have shown similar vulnerabilities. In an attempt to identify factors associated with positive versus negative trial outcomes, a meta-analysis of 106 chronic pain trials suggested that studies published more recently were associated with higher placebo response[2]. This trend has considerable impact on analgesic drug development in terms of overall cost to the sponsors and increased risk of terminating development programmes prematurely due to early failed studies lacking appropriate sensitivity. Efficient methodologies for increasing within-study assay sensitivity and signal detection are high priorities for analgesic drug development, and are discussed below.

Retrospective analyses of clinical trials with antidepressants provide context, with suggestions for reducing placebo response and increasing assay sensitivity that could be applied to chronic pain trials, particularly those focusing on neuropathic mechanisms[3]. Recommendations include the exclusion of patients with mild pain severity and shorter episode duration; maximising reliability, validity and responsiveness of outcome measures; minimising extraneous contact with investigative staff and other sources of nonspecific therapeutic effects; and minimising the number of treatment groups and trial duration. Although intuitively attractive, these recommendations remain largely untested, and the resulting operational and analytic implications are in some cases unknown. However, these analyses also suggested basic changes in study structure, including using placebo run-in periods and flexible-dose versus fixed-dose designs, in which a two-fold greater success rate (and a lower placebo response) has been implied. While the use of a single-blind placebo run-in period for the purposes of enhancing signal detection in a subsequent double-blind study was once considered to be standard in many clinical trials in psychopharmacology, data from recent studies indicate limited utility[4,5]. In brief, studies utilising a single-blind placebo run-in prior to patient randomisation do not appreciably differ in terms of placebo response or in detecting treatment differences, compared to trials that do not use such a manoeuvre.

In contrast, the use of a double-blind, variable duration, placebo run-in period (in which both the patients and personnel at the investigative site are blinded to the length of the placebo run-in period and start of active treatment) has shown better sensitivity in detecting placebo response[5] with approximately three times as many patients in these studies meeting criteria for placebo responders compared to single-blind placebo run-in studies. In this design, all patients continue with study procedures as specified by protocol, but the primary efficacy analyses exclude placebo responders as defined a priori. The notion is that once investigators know the point of randomisation, their behaviour towards a subject changes in a non-random manner. In a similar fashion, there may be utility in withholding from investigators the exact pain criteria (e.g., severity) necessary for study entry. This may prevent investigators (and patients) from inadvertently inflating complaints prior to randomisation, and thus control regression to the mean that can affect placebo response and dull effect sizes. Double-blind, variable duration, placebo run-in periods demand a real-time data management system which can support this operationally cumbersome manoeuvre.

There are several other innovative designs that have shown success in affective disorder trials, which may also increase signal detection and decrease placebo response in chronic pain clinical trials. One is the Enriched Enrollment Randomized Withdrawal (EERW) design[6]. This design differs from classic analgesic study designs by shifting the point of randomisation from prior to receiving therapy to a time after satisfactory efficacy and worst tolerable adverse event levels are established. This design uses an open-label titration period of the active treatment under investigation, more closely mirroring routine clinical practice. Only responders (e.g., those who have shown 30 % response) are then randomised to placebo versus drug. The actual point of randomisation can vary, and a double-blind variable duration run-in period can be used to blind investigators to randomisation time point and baseline entry criteria for pain (although typically the point of randomisation only differs by a few visits). Data gleaned from the pre-randomisation phase can be used to estimate proportions of responders and optimal



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dose in subsequent studies, as well as establish the quantity and quality of adverse events.

Researchers have argued that traditional analgesia trial designs developed for testing compounds in the more homogeneous setting of nociceptive postoperative pain may underperform in chronic pain clinical trials, failing to detect efficacy in particular subgroups because it is masked by poor efficacy in other subgroups. The EERW design has particular utility in proof of concept settings, given its ability to detect effects in a subgroup of patients, and has selective advantages when adverse effects may be problematic, or when there is a strong possibility for separate groups of responders and non-responders, or when initial dose titration is complex or lengthy or must mimic clinical practice. Criticism of the design, however, is also noted, including lack of generalisability to larger populations, and limitations inherent in open-label titration as opposed to randomised titration that might establish effective dosages in a formal manner. Despite these criticisms, EERW designs have shown promise in chronic pain studies using both traditional measures such as pain intensity, and non-traditional measures such as time to efficacy failure. Importantly, this design may require fewer patients than classic designs, providing a more sensitive option for conducting proof-of-concept studies with increased signal detection.

Another novel design that has shown utility in increasing signal detection and reducing placebo response across several psychopharmacology studies is the Sequential Parallel Comparison Design (SPCD)[9]. This design has two phases of treatment; the first phase involves an unbalanced randomisation between placebo and active treatment favouring placebo. In the second phase, only the group of placebo non-responders are randomised to either active treatment or placebo. Placebo non-responders can be defined as those patients who failed to achieve a certain (e.g., 50 %) decrease in their pain scores at a certain visit. The placebo responders can remain in the study in order to maintain the blind, but only the data from the placebo non-responders is used for analytic purposes in the primary efficacy data set. In this way the SPCD can be considered a type of enrichment design in which the population of placebo non-responders is enriched in the final sample. Since placebo non-responders have already essentially "failed on placebo," their placebo response in the second phase of the study is theoretically reduced and the drug-placebo difference in Phase 2 should be greater than in Phase 1 if in fact the compound is active. This analysis method pools data from both phases in order to maximise power and reduce the required overall sample size with increased power (10-20 %) relative to same size classical designs, or the same approximate power with much fewer subjects (20-25 % fewer subjects). The biggest deterrents to the SPCD are the extended length of the trial, increased analytic difficulty due to the creation of multiple data sets, and an overall lack of experience with the operational complexities associated with this design. Although the SPCD is longer than traditional designs in terms of study duration, overall study length expressed as first patient visit to last patient visit may be shorter due to a reduced need for patients and a decreased enrolment period. Modifications to the SPCD involve the use of different test statistics according to equality of treatment effects across the two phases[8], and keeping investigators blinded to the criteria for response and timing of the initiation of the second phase, as discussed above.

Finally, various adaptive designs that increase the probability of trial success by providing more flexibility than conventional designs should play a larger role in analgesia trials. Adaptive design trials are particularly relevant in chronic pain studies, which are characterised by highly subjective and variable endpoints, and a lack of accepted biomarkers which can be used as a short-term proxy for clinical outcome. According to the US Food and Drug Administration (FDA) draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics[9], an adaptive design clinical study is defined as a study that includes a prospectively planned modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study. The relevance of adaptive study design to drug development has been extensively examined, and adaptive designs may more efficiently provide the same trial

information, increase the likelihood of success on the study objective(s), and yield improved understanding of the treatment's effect[10].

Adaptive designs are generally considered to be either exploratory or confirmatory in nature. Two of the most common exploratory adaptive designs are the adaptive exploratory dose-response and the adaptive randomisation based upon treatment response designs. The most common confirmatory adaptive design involves sample size re-estimation. Despite widespread interest in adaptive designs, there have been very few regulatory submissions based on confirmatory adaptive trials, and the majority of adaptive design studies have been in the exploratory realm. Two examples of exploratory adaptive designs are reviewed here.

An adaptive exploratory dose-response design is a common exploratory adaptive design that begins by examining multiple doses across a fairly broad range with the goal of reducing the number of dose groups as the study progresses by utilising unblinded efficacy or safety data in a predefined manner during one or more unblinded interim analyses[9]. Such designs are capable of eliminating ineffective or intolerable doses with minimal patient exposure, and can also suggest additional doses not originally envisioned, as doses for later confirmatory trials need not be limited to the doses studied in the exploratory adaptive trial. Of particular utility are exploratory designs using five to seven doses to ascertain the shape of the dose-response curve, allowing for optimised selection of doses in confirmatory studies for innovative compounds in which dose response relationships are unknown, and where linearity in response may not be appropriately assumed. It is also possible to utilise a biomarker for the interim analysis to determine the adaptive modification.

Adaptive randomisation based upon treatment response is another more frequently used exploratory adaptive design, requiring subjects to be assigned to a specific treatment group based on a comparative analysis of the accumulated outcome generated in the trial[9]. This design is often referred to as a "play the winner" design, with the randomisation schema changing numerous times (if not continually) over the course of a study, necessitating electronic randomisation via Interactive Voice Response (IVR) or Interactive Web Response (IWR), linked to a drug supply that permits different allocation ratios across treatment groups, and clinical trial management systems that facilitate tracking of adaptations. This type of design has been used in dose response studies to steer subjects towards doses that have a higher likelihood of efficacy and away

from drugs that have a higher likelihood of intolerability due to adverse events. A potential problem with adaptive designs such as this is that they can produce changing randomisation probabilities that may violate the balance among treatment groups with regard to important baseline characteristics. To address this concern, the FDA recommends that sufficient patients are enrolled into the placebo group over the duration of the study to ensure that any analysis of response over time (or by study period) can be evaluated fairly. Loading the placebo group with enough patients also helps the study show a treatment effect[9]. Additionally, adaptive clinical trials present qualitatively different considerations regarding the informed consent process, and the ethics of clinical research given that treatment group allocation depends upon accumulated information, as the first patient versus last patient enrolled can have different probabilities for receiving effective treatment[11].

In addition to helping show treatment effects, the importance of allocating the appropriate number of patients to placebo is a key factor in minimising placebo response as patients' expectations of receiving drug influences their response, and imbalance in allocation favouring active medication can be a contributory factor to more favourable placebo responses[12]. Results from a recent meta-analysis of 182 clinical trials in depression have shown that the greatest influence on drug-placebo differences was the percentage of patients randomised to placebo[9]. As the proportion randomised to placebo increased, drug-placebo differences increased. For example, with 50 % of patients randomised to placebo, the advantage of drug over placebo is 50 % larger than when 25 % of patients are randomised to placebo. The logic behind this is evident when considering that adding one patient to the placebo group increases the power for all drug-placebo contrasts, whereas adding one patient to an active treatment arm only increases contrast power for that arm. Appropriate placebo allocation is especially important in analgesia clinical trials where subjective, patient-reported outcomes are prone to moderating variables that lead to heightened placebo responses.

In summary, there are several innovative clinical trial designs and design modifications that may be useful for addressing important issues in chronic pain trials, including heightened placebo response, an increasing number of failed (not just negative) trials, highly subjective and variable endpoints, and a lack of accepted biomarkers. The appropriate application of the above-mentioned designs in chronic pain trials should result in better assay sensitivity, larger effect sizes, and overall increased trial efficiency, ultimately leading to more effective, affordable, and safer pharmaceutical products for patients suffering from chronic pain.

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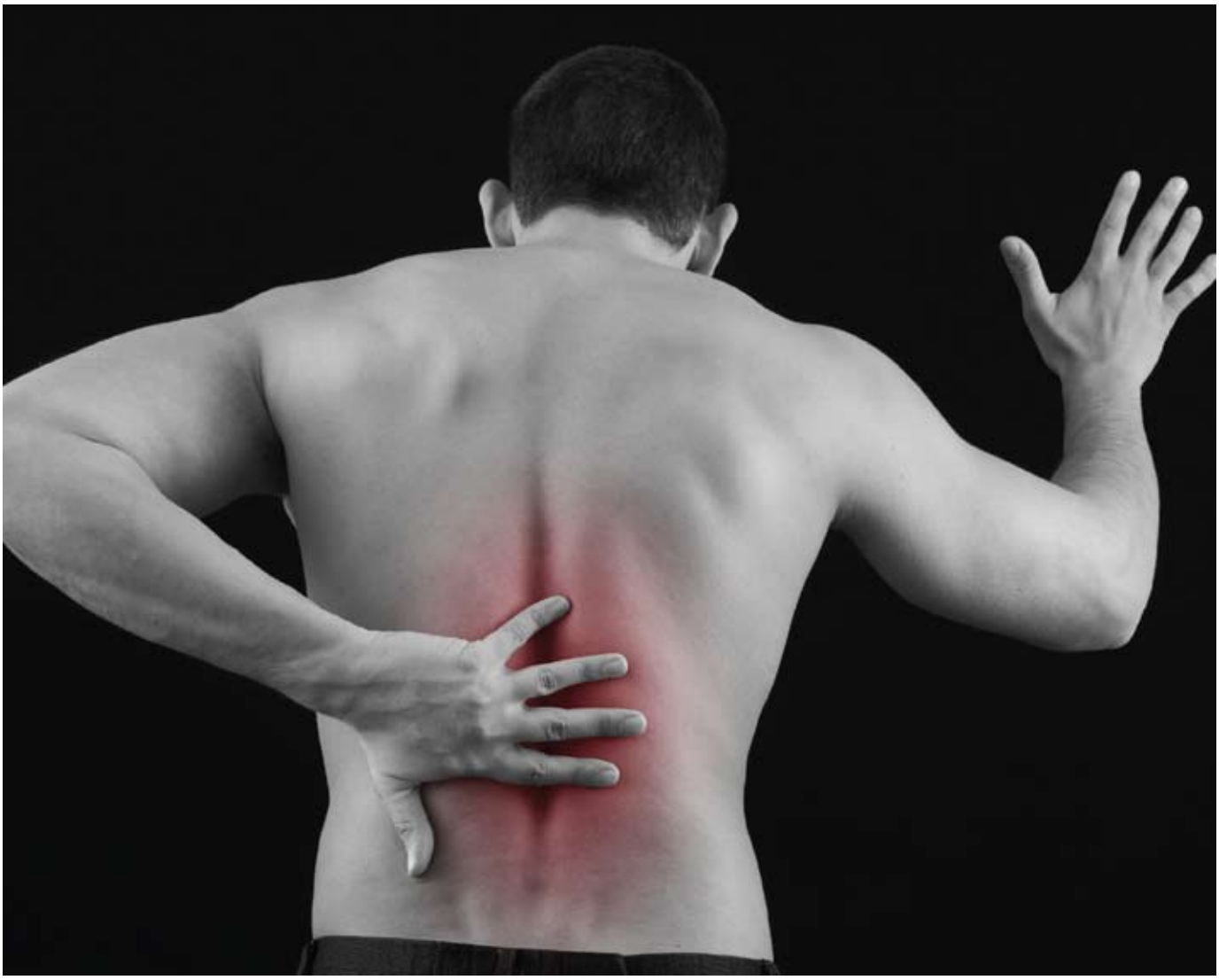

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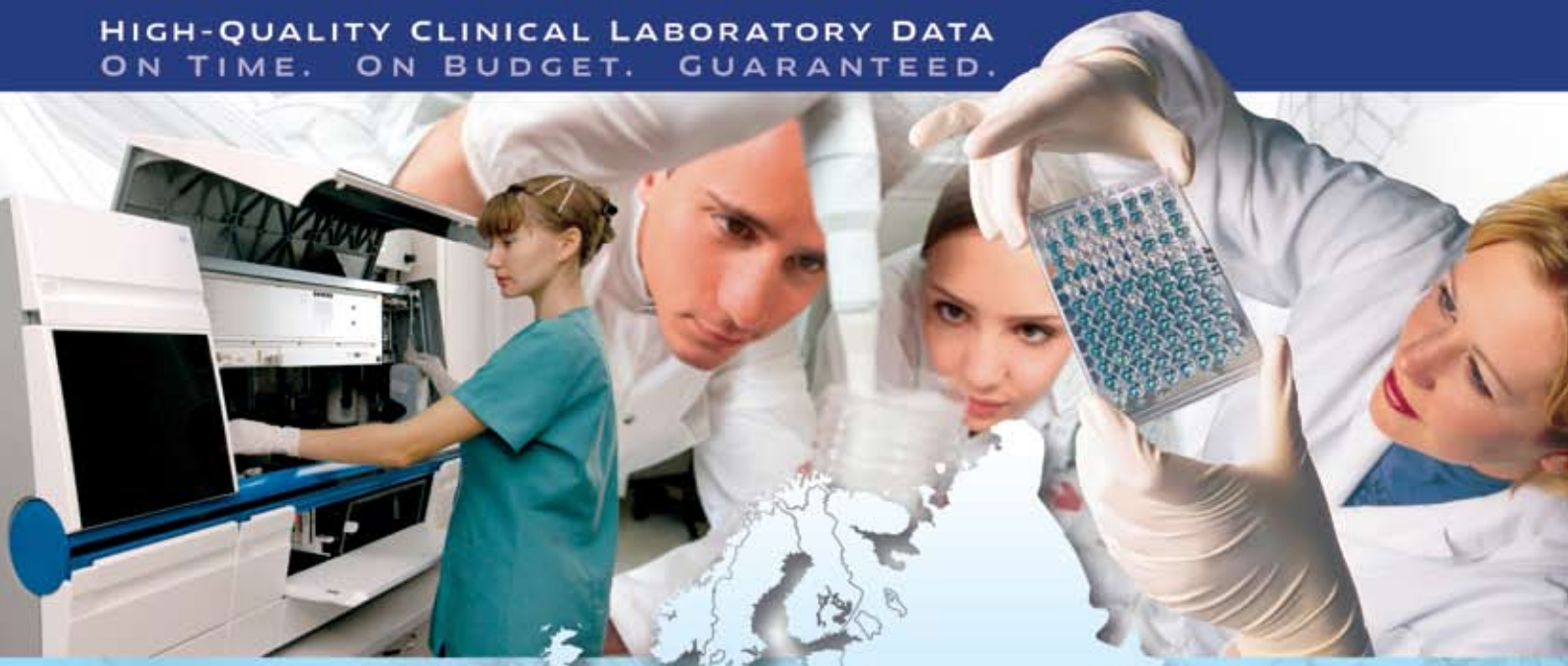

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The Elderly Patient: a Largely Neglected Orphan Population

PEER REVIEWED

People over the age of 65 comprise the fastest growing segment of the world population, with those over 85 leading the way. Especially in the industrialised countries, this tendency will continue due to better social conditions, better control of chronic diseases and improvement of healthcare. By the year 2030, it has been reported that people over 65 will account for an estimated 20% of the US population.[1] In Europe, there will be a significant increase in the number of people 80 and over - "fourth generation" or "fourth age". This age group is expected to rise from 18.8 million today to 34.7 million in 2030 (Eurostat, 2005).

Most of the elderly population maintain their levels of activity and functional status and have a life expectancy that is significant: a 70-year-old with average health has a life expectancy of 14.8 years, and even those with significant co-morbidity such as myocardial infarction have a life expectancy of 8.6 years.[2] Therefore, cure (or even five-year survival) and long-term follow-up are issues of great importance in elderly patients.

The Presence of Elderly Patients in Clinical Trials

Literature reviews have recently shown that older patients are under-represented in clinical trials despite the aging population worldwide. To provide future treatment and optimal care, increased and better representation of elderly clinical research data is needed.

In oncology research, for example, only 22 % to 36 % of patients 65 years of age or older participate in trials for cancer therapy, even though they represent nearly 60 % of the population with cancer.[3-7]

In the cardiovascular area, an appropriate representation of elderly patients in clinical trials has not frequently been observed, but explicit exclusions have even been detected in the past. In acute myocardial infarction (AMI), the exclusion of elderly patients severely limited the ability to generalise study findings to the very age group that most experiences morbidity and mortality from this condition.8 It has been reported that more than 60 % of clinical trials of drug therapy in AMI have excluded the elderly, using upper age cut-offs as low as 65 years.[9]

Heiat A et al. identified 59 major clinical trials for treatment of chronic heart failure (HF) conducted from 1985 through 2000. Explicit exclusion of elderly patients was part of the formal study protocol in 17 of the trials (29 %), even though HF is predominantly a disease of the elderly, with a mean age of 70 years at presentation. These trials accounted for more than 20,000 patients (44 % of the total number of HF trial participants).[10]

Hypertension is one of the most common and important diseases in which treatment has been improved by multiple large-scale clinical trials. Until recently the elderly were excluded, leaving profound confusion for the practitioner on the risk-benefit relationships of antihypertensive therapy in patients aged 70, 80 or older. It is only in the last few years that evidence has been collected demonstrating the benefit of treating high blood pressure in old age.[11-13]

Recently, the organisers of the European project for Increasing PaRticipation of the ElDerly In Clinical Trials (PREDICT) summarised 5280 articles published before February 2008 (357 potentially relevant) in a systematic review.[14] They confirmed that the mean age of participants in clinical trials was much lower than that of real-life users of medications.

In trials for Alzheimer's disease, the mean age of subjects was <75 years, but the incidence of the disease rises substantially over that age. Despite the fact that the prevalence of depression is highest in the elderly, only 9–11 % of clinical trials of antidepressant treatments included older adults. In many clinical trials, co-morbidities constituted frequent exclusion criteria.

Figure 1: Proportion of elderly patients enrolled in trials compared with the proportion of elderly patients in the US cancer population. The differences between the two groups were significant for all age groups (P <.001)

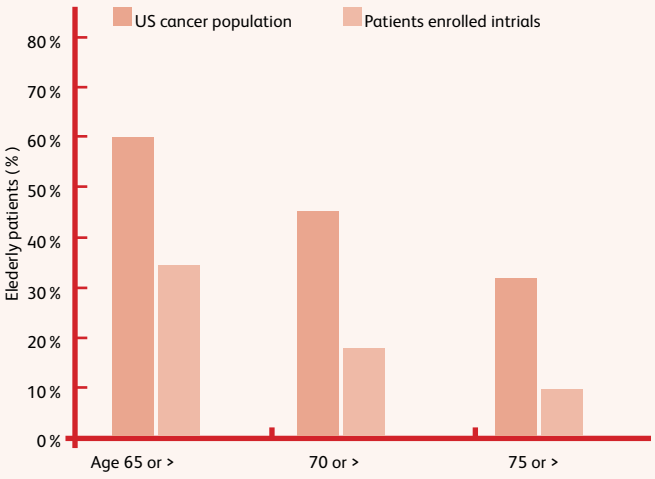
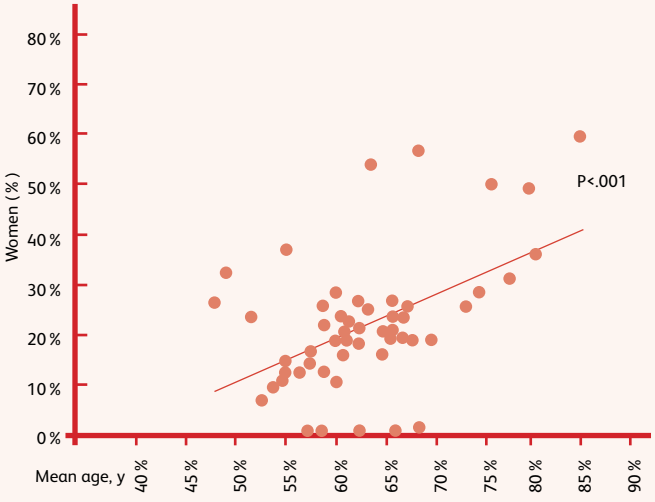


Figure 2: Mean age and participation of women in HF randomised controlled trials



Recent evidence on the effectiveness and safety of medications, therefore underestimates the needs of the elderly, who, in many cases, constitute the majority of users. As a result, study participants often did not represent the average patient in daily practice, and the consequence is that many medical decisions for the elderly are now extrapolations of clinical trial data derived from the younger population.

Chronologic age per se is not a valid criterion for exclusion, and for this reason the FDA in 1989 issued the guidelines that provide support for the adequate representation of the geriatric population in clinical trials.[15] However, physicians are still reluctant to enrol older patients in trials (especially for cancer treatment). The main reasons for excluding older subjects are medical factors (the high risk of adverse effects, presence of co-morbidity or reduced life expectancy); scientific factors (omitting older subjects because they are more likely to be lost to follow-up or in an effort to select a relatively homogeneous study sample or preventing withdrawal due to progressive deterioration of cognitive functions); and medical or socioeconomic patient factors (compromised care, fear of the risks of treatment, difficulties with transport to a study centre, time conflicts, no direct interest of a patient in a clinical trial). [16-17]

The paucity of data from clinical research leads to a vicious cycle of care that is not evidence-based. This underlines the need to generate knowledge by involving older patients in clinical trials.

The "Orphan" Population

Before the enactment of the European Union Paediatric Regulation in 2007, children were considered an "orphan population". The elderly should also be considered in this population group. They are vulnerable, have complex clinical problems, may have a genuine need for more medications and often suffer an inappropriate and often "off label" use of medications. Medicines are prescribed to elderly patients with very little idea of efficacy, dosage or adverse effects.

As clearly highlighted during the recent EFGCP/EUCROF joint workshop (Antwerp, Belgium 2010), the geriatric researchers should tread the path followed by their pediatric colleagues for encouraging drug development for the elderly. In fact, there are many similarities between the paediatric and geriatric populations, and many of the areas of ethical concern are shared by both groups:

- Different reaction to medicines from other adults
- Issues of information and consent (due to mental deterioration)
- Involvement of family and caregivers
- Appropriate age-relevant formulations
- Certain diseases are specific to older people
- Differences in pharmacokinetics and pharmacodynamics compared to younger adults
- Complicated diagnosis (need of a comprehensive geriatric assessment)

Nevertheless, the elderly might also differ from children, mainly for "life priorities"; quality of life and independency are definitively priorities for elderly patients.

Discussions within the Geriatric Medicine Working Group of the EFGCP have recently focused on the best ways to conduct research in elderly people:

1. The elaboration of practical guidelines, which constitutes a priority.
2. The creation of geriatric expertise at the EMA, and also at the ethics committee level.
3. The raising of the upper age of adulthood (or the start of "elderhood") from 65 to 75.

The Need for Harmonization and Further Initiatives

One of the current principal aims of the European Union is to improve practice, rules and regulations throughout the continent. As part of this aim, prescribing for the elderly should be improved and basic geriatric recommendations should be harmonised. Currently, there are substantial differences among geriatric guidelines and geriatric practices in different European countries, and prescribing for the elderly is strongly influenced by differences in drug policies, feedback strategies and national drug formularies.

The organisers of the European project ADHOC have analysed the use and availability of potentially inappropriate medications in older adults undergoing home care in eight European countries (the Czech Republic, Denmark, Finland, Iceland, Italy, the Netherlands, Norway and the UK).[18] They confirmed that the percentage of approved medications in national drug for-

mularies varied across Europe, from 32 % in Norway to 71 % in Italy. Whereas certain potentially inappropriate medications were not available in some national formularies, in other countries they were available but used only rarely, or available and used frequently. Overall the prevalence of their use ranged from 5.8 % in Denmark to 41 % in the Czech Republic, and reflected differences in national drug formularies, country-specific drug policies, regulatory measures and inequalities in the health and socio-economic status of older people. Major recommendations related to the proposition that the appropriate use of medications (including indication, dose, length of treatment, risk modifiers) should be harmonised across Europe.

Besides harmonisation, the following information gaps are still to be filled for the elderly population: proper data about effective dose ranges in acute and long-term use, side-effect profiles, potential for accumulation in the body, drug-drug interactions. Therefore, more regulatory clinical trials should be held in all types of geriatric populations: the performance of clinical trials that have proportionate representation of the elderly would permit the translation of the results to older patients, and allow for direct comparisons of results for younger and older patients who have been treated in similar ways.

The prescription of therapies to the elderly on the basis of trial information obtained primarily from younger, fit patients does not constitute good clinical practice. The collection of evidence-based data ensures that therapies are prescribed to the older patients when they may offer a meaningful gain in survival, quality of life, or both, and avoids situations which may not be beneficial.

Summary

The elderly require particular attention when a drug treatment is prescribed. Global evaluation of their needs and problems, including co-morbidity, polypharmacy, disability and cognitive impairment, is necessary in order to reduce the risk of inappropriate drug use, and appropriately weigh the benefits, the risks of harm, and the cost-effectiveness of drug treatments.

Future research and regulatory measures should focus on specific evidence in older patients; harmonisation of clinical recommendations, drug policies, guidelines and feedback strategies across Europe; and implementation of comprehensive geriatric assessment.

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JCS – speaks with Dan Diaz & Donna Beardsworth of Beardsworth Consulting about OncologyOne

Q. Why Global? Why Now?
A. After 25 years of success as a US based CRO specialising in "complicated clinical trials", Beardsworth, along with many of our CRO colleagues, was challenged by the recent economic trends in our industry to develop a stronger market position in the oncology arena. We felt the best way to respond to this was through globalisation.

Beardsworth's primary focus is in oncology and other complex therapeutic areas for which market conditions and competition for patients are causing many sponsors to look beyond the US for solutions. Beardsworth's challenge was to develop a strategy that responds to our clients' needs in this global expansion.

We felt the best opportunity for growth in this area was to form OncologyOne, which is the result of interviews with clients who expressed the need for experience and expertise as well as flexibility and relationship on a global scale.

Q. How did the Idea of OncologyOne come about?
A. OncologyOne is the innovation of Donna Beardsworth, founder and Chief Delivery Officer of Beardsworth. With over 15 years of global trial experience, Donna understood the industry's need for a global option with oncology trials. Following on the heels of the 2008 economic downturn, the challenge was to develop a value proposition for the mid-size, regional CRO. At DIA 2009, leveraging our connections with fellow regional CROs experiencing the same business and market frustrations, Donna Beardsworth and Dan Diaz met with 22 CEOs and VPs of local, regional ex-US CROs to explore how speciality, niche players can compete on a global scale for oncology specialisation. These initial discussions and follow-up conversations seeded the concept of OncologyOne, and in 2010, OncologyOne's partnership model officially took root.

Q. What Exactly is OncologyOne?
A. OncologyOne is a unified network of niche CROs that specialise in global oncology trials. OncologyOne is aligned under a centralised governance plan that has integrated SOPs, working practices, training and quality procedures under one roof. This 'best-in-class' model translates to consistent quality, rapid implementation/enrolment and more cost-effective strategies for clients. OncologyOne's full service offerings can be customised to meet a client's specific needs on a global scale:

- Protocol development
- Global regulatory affairs
- Medical affairs
- Feasibility
- Site/country selection
- Project management
- Data management
- Monitoring
- Biostatistics
- Medical writing
- Safety
- Programme management
- Safety management platform

Q. What is OncologyOne's Model for Partnership?
A. OncologyOne's model is a partnership of equals among Tier 1 providers, with shared risks, shared standards and accountability along with experience, expertise and expectations of value and quality. The infrastructure is a tiered configuration defined primarily by region and experience, but inclusive of a robust due diligence regarding harmonised SOPs, procedural standards and practices.

In addition to the business requirements, the tier model also differentiates on the breadth of oncology experience and the ability for the partner CROs to deliver on the enrolment requirements. An example is our very strong partner CRO in Australia. However, the ability of Australia to lead a global Phase 3 programme is limited. So for this reason, this CRO is a partner, very much involved in our strategies for success, but at the Tier 2/3 stage.

Generally speaking, Tier 1 partners possess the requisite experience, have passed a QA audit and have a Master Services Agreement (MSA) in place. Tier 2 Partners are engaged with a QA audit and MSA pending. Tier 3 Partners are interested parties at various stages of the vetting process. OncologyOne's goal is to maintain the flexibility of each partner's local country experience while holding to the skeletal strength provided by centralised governance – global reach with local connection.

Q. How do you Maintain/Manage Continuity on a Project with Multiple CRO Involvement?
A. Providing a unique, cost-effective approach to managing the multiplicity of oncology global trials is the guiding tenet of OncologyOne. The partners' depth of oncology therapeutic experience, operations expertise and knowledge of the specific cultural influences in local regions provide a solid foundation for each project. Adding to this depth is the working history and shared experiences between OncologyOne partners for a more effective managerial synergy. While addressing the specific requirements of each project, OncologyOne consistently incorporates continuity management at every level of a project through:

- Centrally led project team
- Integrated technologies through BNet, (CTMS) for 24/7 client access to trial metrics
- Detailed budgets and services listings
- Detailed communication plan with documentation and outcomes
- Regulatory updates
- QA platform
- Vendor/subcontractor selection/management
- Training for staff, investigators and vendors
- eDC platform

Q. How do you Determine the Countries that will Participate in a Project?
A. Besides performing global feasibility, we have developed a process tool that takes in the results of the feasibility along with other considerations such as the regulatory start-up times, costs for the region, and overall numbers of subjects and sites for participation. This more comprehensive up-front approach allows us to determine the best countries/regions to have participate in the proposal process and ultimately in the project.

Q. In what Countries/Regions does OncologyOne Operate?
A. Comprehensive feasibility determines region/country selection including prevalence of oncology indications, standards of care, availability of patients, and experience of prospective partners. OncologyOne Tier 1 partners are currently in place for North America, Western Europe, Central & Eastern Europe, and Russia. Tier 2 partnerships are engaged for South America, Australia, India, and China. Tier 3 partners are in process for Mexico/Central America, Africa and the Middle East.

Q. Why not Begin with India and China?
A. While China and India meet several of our criteria, feedback from our clients was mixed. Many were intrigued by China but voiced concerns that start-up timelines were too long and the level of clinical experience was limited. Likewise, India with its expansive population and reputation for cost-effectiveness is a preferred destination for clinical trials. However, questions of mixed results, inconsistencies in quality and lax regulation need further vetting. Patient safety is an uncompromising standard of OncologyOne.

Q. What Characteristics set OncologyOne apart from Other Global Models?
A. The premise that you have to be an international, "wholly owned" CRO is false, states Dan Diaz, Beardsworth's Vice President, Business Development. "Through my experience at two global CROs, it was common to hear of a strong US team coming to the Bid Defense with much fanfare and background. But when the study was starting and the local CRAs were assigned, it was common for the oncology experience to be limited to the US, thus limiting the team's effectiveness. For OncologyOne, we have been very diligent in selecting Tier 1 CROs that have a deep and broad level of expertise in their local regions. We believe this sets OncologyOne apart since all understand the special nuances of oncology clinical trials."

Global reach
OncologyOne is an alliance of "best in class" regional CROs and technology partners that operate under a centralised governance for consistent quality standards, practices and procedures.

Local oncology experience and connection
OncologyOne provides all the strategic benefits of a global CRO with the added flexibility of local oncology expertise. This translates to an immediate resource for in-depth knowledge of the local oncology marketplace and the interconnected local structure necessary to provide an effective and economic global trial solution.

Patient-centric focus
OncologyOne understands the cancer patient and the local investigator sites. Extensive experience in oncology trials means access to local oncology experts and established relationships with proven sites for patient recruitment resulting in:
- Accelerated patient recruitment
- Quickly met enrolment targets
- Fewer non-enrolling sites
- Global enrolment strategies

Project Management Continuity
There is a single point of client contact in the Central International Project Manager. Project continuity is also ensured with a detailed communication plan – a requisite for each project that includes client-/project-specific requirements.

Access to Executive Management
A senior executive is an integral and active member of each project team along with medical experts.

Dan Diaz, Vice President Business Development at Beardsworth has worked in the Pharma and CRO industry for over 24 years. Starting his career with the former Merrell Dow Pharmaceutical company, he specialized in respiratory medicine and hypercholesterolemia. His business expertise spans contracting with government entities, small & global Pharma, Biotech companies, niche CROs and SMOs in all phases of clinical research. Currently, Dan is leading the global growth strategy with the launch of "OncologyOne" a new global oncology niche initiative.
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Donna E. Beardsworth, MA, Executive Vice President and Chief Delivery Officer. Donna has worked at the investigative site level, the sponsor level, and at the CRO level in all aspects of clinical drug development processes. Donna heads both the Executive and the Senior Management Teams at Beardsworth and is the Chair of the Advisory Board. Donna was named Entrepreneur of the Year in 2002 by the Hunterdon County Chamber of Commerce and is a past President of the NNJ-ACRP Chapter where she currently serves as a trustee.
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Respiratory Diseases in Children in Russia and Ukraine: Etiopathogenesis, Clinical Picture, Clinical Research and Legal Problems

Numerous epidemiological researches indicate that each child tolerates an average of 3-5 instances of acute respiratory diseases (ARDs) within one year. Thus most often acute respiratory infections occur in the case of infants, preschool children and primary school children. Children aged 10 years old and elder suffer from acute respiratory diseases 2-2.5 times less often than children aged up to three years old. It has also been established that 15-40% of children suffer from respiratory infections much more often than their contemporaries, and account for 67.7-75% of all cases of ARD.

It is accepted that children subject to frequent respiratory infections are known as sickly children (SC). Herewith special attention is reserved for children whose respiratory infections are characterised by a long illness.

Frequent and especially severe coursing acute respiratory diseases can lead to the loss of physical and psychological development of children, and can promote the reduction of functional activity of immunity and the failure of compensatory adaptive mechanisms of an organism. All of these can promote the early onset of chronic inflammatory processes in respiratory apparatus, including bronchial asthma. Recurrent respiratory infections can also lead to maladjustment of a child because of isolation from contemporaries and absence from school. There is need for considerable material resources in the case of frequent and long acute respiratory diseases in children, which can lead to economic damage directly associated with the costs of treatment and the loss of parents' working time.

Infections of the respiratory tract are among the widespread pathologies of children, occurring basically in winter. Recurrent infections of ear, nose and throat (ENT infections) in the case of children, particularly rhinopharyngitis and otitis, represent a serious problem for the public health services because of the high frequency and risk of complications. The highest incidence of disease is within children aged up to two years old, and it decreases during the process of immune system maturation. There is a need for public health resources for these diseases, which are one of the important causes of temporary disability among parents, which also accounts for their significant economic impact.

Recurrent ENT infections are usually defined as the presence of three or more events of acute diseases in a period of six consecutive months, along with up to 10 events of diseases during one season. Most of these infections are caused by bacterial agents, and can usually be successfully treated by antibiotics. However, the risk of complications and serious consequences of diseases increases with the number of acute events. So, in the case of children suffering from recurrent otitises media, residual damage of the middle ear involving partial or constant loss of hearing are possible, which can also lead to deterioration of speech development, and to cognitive or psychosocial disorders.

Great importance is given also to features of formed immunity in terms of the causes of frequent respiratory infections. Children aged 5-9 years suffer most frequently. Up to 11 years of age, the incidence of infectious pathology of respiratory apparatus considerably decreases, by a factor of two. It has been established that frequent respiratory diseases with mainly severe recurrence (three times or more per year) and mainly oligosymptomatic recurrence (five times or more per year) occur also in the cases of children with no centres of pulmonary or extrapulmonary chronic infection. This group is rather considerable, constituting 0.9-1.2 % of the children's population. Thus the conventional actions of primary prevention of respiratory infection (vitamins, adaptogens, etc.) for this group of children appear to be insufficiently effective.

Flu and acute respiratory viral infections (ARVIs) remain the major problem for children's public health services, being the most common form of infectious diseases in children's infectious pathology. In the conditions of a megalopolis with clearly defined processes of migration and density of population, the risk of episodes of respiratory infections is extremely high. Children whose immune system is at formation stage, in particular children visiting organised groups (schools and preschool centres) are especially predisposed to various ARDs. It is known that the child aged 5-6 years old tolerates acute respiratory diseases three times more often (per year) than the healthy adult person.

Flu and ARVIs remain the most widespread diseases of children. According to data from the Ministry of Healthcare (MHC) of the Russian Federation, from 27.3 to 41.2 million patients are annually registered in Russia. The problem of ARDs is also aggravated by the fact that repeated diseases promote occurrence of chronic bronchopulmonary pathology, and are the cause of acute and chronic maxillary sinusitis (highmoritis), sinusitis, tonsillitis, otitis, and can form an allergic pathology, and lead to secondary immunosuppression.

In the beginning of the third millennium the most widespread diseases of children are allergic diseases. According to the data of native and foreign authors, up to 10 % of children suffer from bronchial asthma, and up to 20 % suffer from atopic dermatitis (eczema), and the steady growth in numbers of such patients from year to year is observed everywhere.

The basic therapy of allergic diseases means the long application of anti-inflammatory inhalation drugs (glucocorticoid steroids) for children with a respiratory allergy, and antihistaminic, drugs, which targets are different mediators, in the case of skin allergic manifestations.

However, considerable changes in the functioning of various elements of the immune system are revealed as a result of immunoassay of patients with bronchial asthma (BA), atopic dermatitis (AD) and dermal respiratory syndrome (DRS). Hence, during discussion of possibilities of therapeutic correction of the revealed immune disorders, clinicians should use those immu-

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notherapeutic drugs or methods which allow differential influence of various elements of the immune reaction. Moreover, recurrent respiratory infections are a big problem for children suffering from an allergy; the combination inevitably causes an aggravation of allergic disease.

ARVIs have remained the most frequent causes of development of acute obstructive bronchitis in children till now. A direct correlation between frequency of cases of ARVI and the number of events of aggravation episodes of recurrent bronchitis in children has been established. The prediction after a single occurrence of obstructive bronchitis is usually good, however, according to Tatochenko (1998), 35-50 % of such children have repeated cases of obstruction of the upper airways. The majority of relapses are observed within 6-12 months after the first obstructive event, and develop as a response to a new respiratory infection. If the child has a chronic infection promoting development of a secondary immunodeficiency, then the prediction considerably worsens. One of the directions of reduction of growth of bronchopulmonary pathology in the case of children is medicamentous prophylaxis of new aggravations. Unfortunately, rehabilitation methods used until recently are rather ineffective and do not provide ultimate recovery of the child.

It is known that recurrent bronchitis has three variants. Recurrence of bronchitis stops spontaneously in 50 % of cases. Bronchitis relapses in one-third of patients occur constantly over a number of years. Children whose bronchitis is diagnosed at early and preschool age suffer somewhat longer. According to Artamonov (2001), recurrent bronchitis transforms to asthma in 12.7 % of cases, and to bronchial asthma in 2 % of cases.

Considering the high risk of repetition of an acute obstructive bronchitis the group of children having an additional risk factor of chronic inflammatory process development - presence of the centres of a chronic infection (in the form of tonsillitis, adenoiditis, rhinosinusitis, pharyngitis) is defined.

Clinical research is vital to promote medical knowledge and improve medical care. In children, clinical trials have resulted in significant improvements in their healthcare. An example is childhood acute lymphoblastic leukemia, in which the conduct of multicentre clinical trials has improved the five-year survival rate from 25 % to more than 70 %. Children and adolescents represent about 25 % of the European population; however, most medicines given to children are used off-label. In hospital paediatric wards this is around 45 %, and in the neonatal intensive care setting this can be as high as 90 %. The experience gained in this way is rarely incorporated into clinical practice guidelines or medicinal product labelling. This off-label use of drugs in children represents a danger to the child in terms of potential underdosing (and possible lack of efficacy) and/or overdosing (with resultant toxicity). The lack of appropriate pharmaceutical formulations to allow the effective and compliant administration of many drugs in children is a further issue.

Legal Problems of Carrying out Research on Children

During the conduct of children-aided clinical researches, as well as ethical standards it is necessary to know the legal norms regulating the issue.

Nowadays the following standards are used as a legal basis for carrying out children-aided clinical researches in Russia:

- Declaration of Helsinki (2001);
- Constitution of Russian Federation;
- The Basic Law on the Health Protection of the Citizens of the Russian Federation from 22 July, 1993. No.5487-1 (with changes from 20 December, 1999);
- Federal Drug Act from 22 June, 1998 No.86-FA
- Branch standard OST 42-511-99 'Good Clinical Practice in Russian Federation' (stated by MHC of Russian Federation 29 December, 1998);
- Orders and instructions of Ministry of Healthcare of Russian Federation.

The Basic Law on the Health Protection of the Citizens of the Russian Federation defines the rights of minors during realization of medical intervention, including biomedical researches, as follows:

1) Point 5 of article 24 'The Rights of minors' it is specified that minors have the right to get all the necessary information about the level of health in a form which is understandable for them;
2) In the same article it is stated that minors older than 15 years have the right to free informed consent to medical intervention or to renunciation of it...

Article 43 of the Basic Law of the Russian Federation, regarding regulation of biomedical researches, states: 'Diagnostics, treatment and drugs which are not approved but are under consideration in accordance with established procedures can be used for treatment of persons up to 15 years old only if there is a direct threat to their life, and only with the written consent of their lawful representatives'.

Article 40 of the Federal Drug Law accurately explains carrying out clinical researches on children.

Point 1: 'Participation of patients in clinical researches of drugs is voluntary.'

Point 5: 'Clinical studies of drugs on minors, except in cases when the investigated drug is intended only for treatment of children's diseases, or when the purpose of clinical studies is acquisition of data about the optimal dosage of a drug for treatment of minors, are not tolerated. In the last case, clinical studies of drugs on adults should be carried out prior to clinical studies on minors.'

Point 6: 'During the conduct of clinical studies of drugs on minors, there is a need for the written approval of their parents.'

Point 7: 'Carrying out clinical studies of drugs on children, which don't have parents, is not approved.'

It is necessary to draw attention to the Declaration of Helsinki among other international norms. The Declaration of Helsinki states:

- The national law can approve carrying out the study on invalids if such research will not lead to direct advantage for their health, only in cases when such a study is useful for persons of the same category and when the same result cannot be achieved on persons not belonging to the given category;
- In the case of studies on insane persons the approach can differ. The person can take part in a non-therapeutic study if participation in this research bears no more than minimal risk and does not contradict the interests of the person. In terms of philosophy it is ethical to allow a child to take part in a study

only in the case when the risk has only a minimal value – risk is no greater than expected under usual conditions.

The Clinical Trials Directive (2001/20/EC) is a legislative instrument aimed at providing a homogeneous legal, ethical, and scientific context for the conduct of clinical trials in the EU, and was expected to simplify clinical trials and, therefore, stimulate clinical research. However, its implementation has not yet had a positive effect on the number of studies being conducted in paediatrics.

In January 2007, the European Medicines Agency (EMEA) introduced a new paediatric medicinal products regulation. It requires that all medicinal products for which a new marketing authorisation application will be made, or existing drugs covered by a Supplementary Protection Certificate (SPC) where a variation to the license will be requested, have to be studied in children according to a Pediatric Investigation Plan (PIP). This has to be agreed on with the EMEA's Pediatric Committee (PDCO), in order to generate either positive or negative data that will be mentioned on the label. A waiver to conduct studies in all or some of the paediatric population can be granted if the medicinal product is expected not to be safe or effective in children, if the indication does not occur in children, or if the product is not expected to represent a significant therapeutic benefit over existing products used in children.

It is noteworthy that the EU implemented the paediatric law as a regulation, i.e., as directly effective European Law that cannot be modified by national authorities. This ensures consistent requirements within the entire EU, which may encourage the conduct of studies throughout the EU in children. In contrast, the Clinical Trials Directive was implemented by the national authorities with some country-specific modifications that led to some delay in coming into operation in several EU countries, and also to some inconsistencies in requirements between countries.

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EDC Studies Need New Model of Leadership

Electronic data capture (EDC) has become the norm for new clinical studies. Therefore, it is now critical to understand how using EDC changes the way we work. Many papers and presentations have focused on how EDC forces the study team to prepare for study setup earlier than they would have done for a similar study conducted on paper. The EDC start-up timeframe is loaded with deliverables that could have waited a few weeks or even months to be completed in a paper world. In an EDC study, most of the deliverables are now due long before the first patient is enrolled. The people and tools that are used to oversee these deliverables and deadlines are major contributors to the success of the study startup phase, and help to ready the project team for a study that will be successful in duration.

In the world of EDC studies, success is defined more by utilising the right processes and people, and is less about the software system selected. Most EDC vendors would probably disagree with that statement, and there are examples where one system would be suggested over another based on certain project needs, budgetary constraints and perhaps other study requirements. However, the minimum requirement of EDC software is to capture, view, edit and manage data from a clinical trial. Most of the EDC tools in the marketplace offer these basic functions, with many having advanced levels of functionality to make the software unique. Therefore, almost any EDC software that is regulatory-compliant would be a workable solution for collecting data for a clinical study. Software on its own, though, will not make the study a success. The team wrapped around the system needs to be available, interested and accountable. The processes used during the setup, conduct and closeout of the study have to be clearly articulated, consistently used, well documented and properly managed. A structured, easy to follow, easy to understand methodology needs to be utilised, and someone needs to ensure the software is being properly purposed for all types of users, including Clinical Research Associates (CRA's), data management, project management and investigator site staff. Conducting an EDC study efficiently needs different leadership compared to a paper study. In our organisation, we call the person that oversees an EDC study implementation the technology project leader (TPL), however similar titles exist in other companies, such as the technology project manager, data management project leader, or data management team leader. The title is not what matters. What matters is the role that this resource plays in the methodology of conducting an EDC study.

For any clinical study, but particularly an EDC study, the start-up phase is typically a time that is very critical to getting things done correctly and on time. It is also the part of the trial that is the busiest for all project team members. This is the time, therefore, that should receive more attention in an EDC study as well as more resources, though not just any resources. The additional resource needs to be someone who can facilitate the study start-up process, someone who can help promote communication across the team functions, someone to pay close attention to the study timelines and deadlines, and someone who can provoke other staff to pay attention to details and to accomplish EDC-related tasks efficiently and on time. Many organisations, both sponsor and CRO, would suggest that this role falls primarily to the clinical study leader or project manager (PM). It is our opinion that the clinical PM has many other responsibilities during study start-up that are focused solely on the clinical aspects of the study. Adding aspects for all technology utilised in a study does not make effective use of the clinical PM's expertise. For example, the process of setting deadlines and timelines for the build of an EDC study, including electronic Case Report Form (eCRF) design, edit check development, user acceptance testing schedules and training delivery plans are critical steps in the start-up phase of any EDC study from a technical perspective. Managing this process requires constant supervision, and knowledge of what each team member is required to do in a technology deployment, what function is required, and at what time. The PM should be more concerned and focused at this study start-up time with site selection, site contract negotiations, budget tracking for the study overall and CRA selection, training and management.

The initial tasks listed above are technical steps in building an EDC study. The next tasks are clinical steps in building any clinical trial, and are an integral part of what project managers do for any study, EDC or paper. These are the critical items a hiring manager would look for in a clinical PM. For an EDC study, the PM should retain all overall project management responsibilities, but in order to place the proper amount of focus on the technical aspects listed in the first set of steps above, delegation of those technical aspects to someone else is helpful and often necessary.

It is important to note that this supporting project management resource (called the TPL for the remainder of the article) does not work as a separate entity focused solely on the EDC aspects of the study. Rather, they are the catalyst for communication across the functions of the study start-up team. They are focused on ensuring all departments working on the study are not working in silos, but are sharing their progress, successes and issues across the team.

Task 1: Setting the Plan

The first area of focus for the TPL is creating the EDC project plan. This plan is the blueprint for all steps, tasks and resources that will be needed and followed in the entire build and deployment process. At a minimum, it should include the following items:

- Internal meeting schedule
- Roles and responsibilities during build process
- Roles and responsibilities chart for EDC tasks in the system

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- Integration plans for any internal and/or external integrations
- UAT dates and resources assigned
- EDC training plan for project team
- EDC training plan for investigator sites
- Timelines for all deliverables

This project plan should easily be inserted into the overall study project plan managed by the clinical PM. It should literally be dropped into the plan developed for the study itself, as the EDC setup is just one step in the total study setup process.

The clinical PM is kept up to date on the progress of the EDC build in two ways. The TPL is included in the clinical meetings during the setup phase of the study, and provides weekly (or as needed) updates. Secondly, the clinical PM and their clinical project team are required to provide input at various critical time-points during the EDC build process (eCRF screen design review, edit check specifications, user acceptance testing and again, just prior to go-live). Therefore, the TPL should provide training for the project team early enough in the project so that the clinical team can help make decisions with the study design. This interaction between the TPL and clinical PM will help to ensure that all parties accomplish their go-live goals and will set the clinical team up for success once go-live is reached.

Task 2: Managing Technical Resources

There are many roles utilised in an EDC study that are typically seen as "back-end" resources. This refers to staff who work behind the scenes, not usually client-facing (internal and/or external), and who manage their workload by the number of uploads, debugging sessions, critical faults and system errors they encounter in a day. These are the technical gurus of the programming, database structure and configuration specifications. These resources often prefer to be behind the scenes, and are happiest when talking bits and bytes. A resource that can combine technical competence with strong leadership in a team environment will help to cross the bridge between clinical jargon and technical jargon. The TPL is basically the translator needed between these two areas to ensure effectiveness of the EDC application. The TPL is critical in giving the programming team the information needed on clinical issues within the protocol, and how they should be translated into the eCRF screens and the edit check programming. Most of this information will come from the clinical and data management teams, and often this can be communicated directly between them and programming, but the TPL adds a timeline and deadline perspective to those conversations. The repercussions and risks associated with these tasks/deadlines need to be addressed and enforced, as any slippage will cause issues to the overall EDC project plan, and therefore the overall study schedule as well. The TPL is therefore the conduit to transfer the proper information and the ringmaster to motivate and challenge the team to meet (or beat) the deadlines for the project.

Task 3: Managing and Ensuring Accountability

Reaching go-live on time and on budget is sometimes seen as the endpoint of an EDC study. In some organisations the role of the TPL would end at go-live. We believe that the role of the TPL is reduced once go-live is achieved, but their job is not yet complete at this time-point. At go-live, several of the building functions are complete, but it is at this time that the role of the CRAs, data management, clinical PM and investigator site staff become even more important from an EDC perspective.

The site staff must be trained in the EDC tool being used, and it assists in data collection if they are motivated to achieve results. CRAs are the best resource to motivate the sites, and they in turn need proper training to assist the sites as needed. Here is where the TPL can assist again. The TPL has been involved with the technical development of the system as well as in the clinical decisions of the system and how those decisions have been employed in the EDC technical design, therefore the TPL is best suited to develop the proper training programme for both the sites and project team staff.

Sometimes we hear in the field that a site doesn't like an EDC application being used. However, nine times out of ten this is because the training programme employed for that study was

either not timely or not sufficient for the user. It is rarely because of true defects with the software. The project team needs to have a full understanding of how the sites will enter the data and answer queries, as well as the functions specific to their job role, such as creating queries and source data verification. As go-live is reached and data is entered into the system by the sites, the project team members need to fully understand the workflow required, and need to complete their review and tasks in a timely fashion. It is at this time-point that the TPL attends clinical calls to emphasise proper remote monitoring skills. Data collected but not monitored in a timely fashion reduces the overall effectiveness of EDC. Project teams will recognise the benefits of the EDC system only if they are using it properly and consistently. In this way, they are able to notice trends and issues and alert the site staff prior to the trend getting out of hand.

We have focused on CRAs and monitoring tasks, but the commitment to reach maximum effectiveness with your EDC study needs to reach all staff involved with the study, including (but not limited to) project management, quality assurance, medical monitoring and pharmacovigilance. Knowledge is power. All of these areas can benefit from the use of EDC if they fully understand how the system works with respect to the information they need and the data being collected.

The role of the TPL is a varied one. Three areas were highlighted where the TPL makes a true difference in the life of an EDC study. The job requires a person with a skill set that includes technical abilities, time management abilities, supervisory abilities, powerful communication skills and a strong commitment to quality. The TPL is a driving force to generate positive attitudes across the study team, helping all project staff maximise the effectiveness of the EDC system deployed. Successful EDC studies are not just about the software selected. Successful EDC studies are about the process wrapped around the software, the people that manage that process and additional specialised support for the project manager. Successful EDC studies require this different model of leadership.

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Cool Chain and Clinical Trails

PEER REVIEWED

I quite often see articles written on cool chain and articles written on clinical trials, but there aren't many that integrate the two together. This piece will discuss the current problems that exist in running a clinical trial in an emerging country such as Russia, Brazil or India – and the cool chain issues that will inevitably be encountered in these climates.

The key factors in cool chain management of clinical trials are efficiency (speed), value of information and easy to use systems – making the gathering and analysis of data easy and reliable.

Firstly, I will explain the 'cool chain':
A cool chain (or cold chain) is a supply chain along which a product's temperature is maintained from the point of manufacture until its end use.

Cool chain is a core element in the transportation of temperature-controlled pharmaceutical product. Most cool chain products need to be stored between +2˚C and +8˚C for stability and in accordance with regulatory body requirements. These temperatures are usually the 'magic numbers' in the industry. Cool chain is an expanding part of the industry and will continue to be so given increasing compliance requirements. This, coupled with larger numbers of new drugs in clinical trials and R&D requiring chilled temperature control in storage, means a potentially prosperous future for temperature-controlled logistics.

Temperature-controlled supply chains are not always 'cool'. Some products have to be kept frozen – this is often achieved by packing with dry ice. Other products must be kept warm – often this means a room temperature band of something like +15˚C to +25˚C.

So, that's the 'cool chain' – a chain of transportation ensuring that the product travels at a desired temperature to preserve its qualities.

Why is cool chain so important in clinical trials?
To explain this, it is important to understand what a clinical trial is, its different stages and how much of the world one clinical trial can cover:

Clinical trials are most commonly performed to analyse new drugs, medical devices, biologics, psychological therapies or other interventions. They are a requirement before the relevant national authority approves marketing of the drug or device. There are several different types of clinical trial:
Prevention trials – testing new approaches that doctors believe can lower the risk of developing a disease
Screening trials – testing the best way to find a condition/disease in its early stages
Diagnostic trials – testing better procedures for existing diseases or conditions
Treatment trials – testing new medicines or new approaches to surgery/therapy
Quality of life trials – ways to improve comfort and quality of life for patients (e.g. incontinence drugs)
Compassionate use trials – treatment option for patients suffering from a disease for which no satisfactory, authorised alternative therapy exists

There are **four phases to a clinical trial** involving new drugs, and each phase of the drug development process is managed as a separate clinical trial. These phases are usually known as:
Phase I studies
Phase II trials
Phase III trials
Phase IV trials

Phase I Studies
This is the first stage of testing in humans. Normally, a small (20-100) group of healthy volunteers will be selected. Phase I studies most often include healthy volunteers, however, there are some circumstances when real patients are used, such as cases where patients have terminal cancer or HIV and lack other treatment options (compassionate use trials).

Phase II Trials
In these, the potential drug is tested in around 20 to 300 volunteer patients suffering from whatever condition the drug is to potentially treat. They are designed to show whether the drug is safe in the specific patient population and to look for signs that it might be effective.

Phase III Trials
If Phase II trials are successful, then the potential drug will undergo Phase III trials, which are widespread multicentre trials on at least 300 to 3000 patients in clinics to test the efficiency of the product. They are usually randomised and double-blind (this is where neither the patients or the researcher know who's being given the active drug).

Once Phase III trials are completed, the drug is filed with the relevant country authority for review. In the UK, this is the Medicines and Healthcare products Regulatory Agency (MHRA); in the US, it is the Food and Drug Administration (FDA); in Australia it is the Therapeutic Goods Administration (TGA) and in Japan, the Ministry of Health and Welfare. Some Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly life-saving drugs until the drug can be obtained by purchase. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

Phase IV Trials
After the drug is launched, further Phase IV studies are carried out to monitor possible adverse reactions or other responses

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when large numbers of patients begin using the drug.

During the 'drug pipeline' or 'drug discovery process' drugs may also go through a 'pre-clinical studies phase'.

This stage of the drug development pipeline is a study to test a drug, procedure or other medicinal treatment. They involve in vitro and in vivo experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information. The aim is to collect data in support of safety. Pre-clinical studies are required before clinical trials start.

So, as you can see when coordinating shipments from a clinical trial, the need for cool chain assistance is heightened.

It is understood that drugs that are intended to be used on humans, must be tested on humans to ensure they are safe for use. It is due to this fact that quite often the samples taken are blood or tissue samples, and need to be sent to the research laboratories quickly, efficiently and undamaged. It is well known that the different stages of clinical trials can take place in many different global locations. This makes the 'need for speed' and temperature control even more vital.

For example, the drug could be created in a university in Poland, administered to the patient in a hospital or clinic in Africa and the sample be sent to a research laboratory in India or China. This is a very long chain of transportation where the drugs and samples will experience a variety of different climates. Appropriate cool chain packaging measures must be in place to ensure the shipment arrives at optimum viability.

Emerging Countries

We have all read the articles and seen the trend emerging – where countries such as India, China, Russia and more recently many African countries are becoming hotspots for conducting clinical trials. Just last month in this publication there was much conversation about Australia and the Caribbean being the 'ones to watch' in clinical studies.

The popularity of these countries only amplifies how 'international' a clinical trial can be. And it is this 'internationality' that is really beginning to test the cool chain. Samples need to be sent quickly, efficiently and carefully to ensure they arrive at their destinations in a usable state, i.e. in perfect condition.

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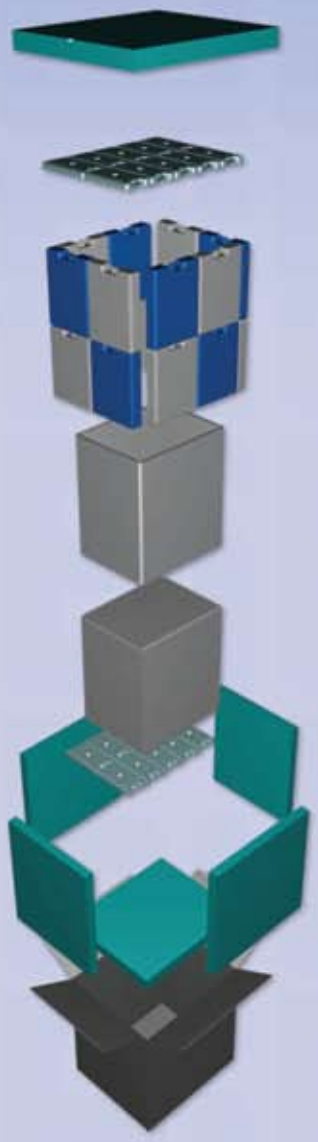

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Building Successful Supply Chain Solutions in Clinical Trial Supplies

PEER REVIEWED

Recent merger and acquisition models have had an impact, and continue to do so, on the number and ways drugs are being developed, and the supply chain solutions required to support clinical trials. The "mega-mergers" have led to rationalisation of pipelines and staffing, but are still operating under the traditional "large pharma" model. Other strategic acquisitions have led to an alternative model of "satellite-affiliates" continuing to drive development as agile focused smaller business units. The global recession and the impact of fiscal constraints have also led to more conservative clinical development plans for biotech and virtual pharmaceutical companies wishing to delay the potential pitfalls of late phase drug development. Add to this the continued interest in non-commercial trials and the movement towards sites in the emerging markets, and it can be seen that supply chains are becoming more complex than ever before. While some of this may paint a gloomy picture, the fact is that all companies developing and marketing drugs need to show a healthy R&D expenditure to assure themselves, and their investors, that they have pipelines that will potentially replace current revenues of drugs as they move off patent. The clinical drug development industry continues to grow at a healthy rate across the board with many elements, including clinical supplies packaging, seen as non-core activity, using outsourced supply chain solutions.

Common objectives of teams working in drug development judge the execution of a clinical trial as successful when the project is finished on time and on budget, and has a high level of quality built into the processes and generated as trial data. The objective of building successful clinical trial material supply chains should be clearly defined before initiating any project to meet these three pillars of project success whilst overcoming the challenges in clinical trials outlined below.

Whether a sponsor has an insourcing or outsourcing model for clinical supplies activities, it is essential that the assembly and management of trial material supply chains meet these objectives. Elements to consider are:

Active Pharmaceutical Ingredient (API), drug product and comparator manufacture location

Packaging specifications to protect the product

Packaging requirements to enhance patient compliance

Labelling requirements to meet all local regulatory requirements

Country language text or final label formatted text included in the Clinical Trial Application (CTA)

European Qualified Person (QP) and other regional regulatory release requirements

Warehousing and distribution strategies to meet regulatory requirements

Supply chain Good Manufacturing Practice (GMP) certification in support of CTA application

Supply chain team reporting structure

Supply chain team interaction with trial reporting tools

Once the clinical trial protocol is drafted, countries or regions for the study are selected. Bulk drug manufacture location is known, and key clinical/sponsor team locations are identified. Many elements for building the most appropriate clinical material supply chain are in place.

Often the locations of API and Chemistry and Manufacturing Control (CMC) manufacture during development have limited flexibility. So the main options for building flexibility into a clinical material supply chain will be where the clinical supplies packaging takes place. Ideally, a number of alternative labelling approach options, pack designs and packaging locations should be available for consideration. Building global supply chains that will be successful can be difficult if the number of alternative options is limited. If the study forms part of a programme it is paramount to consider synergies of the individual study requirements to other studies in the programme.

When the supply chain for one protocol resides within a programme of studies, the option to pool as many stages of manufacturing, packaging and assembly of the clinical supplies across protocols becomes more and more compelling. If the correct packaging, labelling and kit designs are used, the benefits in cost and flexibility of stock by sharing blinded bulk drug, comparator and placebo, packaged bright stock, label designs and even complete multi-protocol labelled kits across protocols can be great. However, the real benefits are not realised until forecasting across protocols is shared with the supplies group to allow appropriate inventory levels to be continually maintained by the global project management team.

Key questions that arise for both specific studies and a program of protocols are:

What is the country/site initiation plan?

Is there going to be a need for a centralised/global or regional approach to labelling and packaging due to specific regional/local comparator requirements?

Is there an economy of scale in centralised packaging for a study or pooling across studies for specific parts, or all, of the packaging supply chain?

Is it preferable to perform the labelling and packaging close to where the bulk drug is already and distribute kits globally in bulk, or ship the bulk drug to a packaging location closer to where the majority of patients are projected to be recruited?

In many instances today the packaging segment of the supply chain still takes place at a location close to the sponsor's key decision-makers. The convenience of their location over cost and with a potential delay in shipping is chosen, rather than sending the bulk to a clinical supplies facility closer to the location where the majority of patients will be recruited. Packaging supplies close to the patients also means that once the packed kits are released they are immediately available to ship over a shorter transit time to clinical sites. However there is a downside

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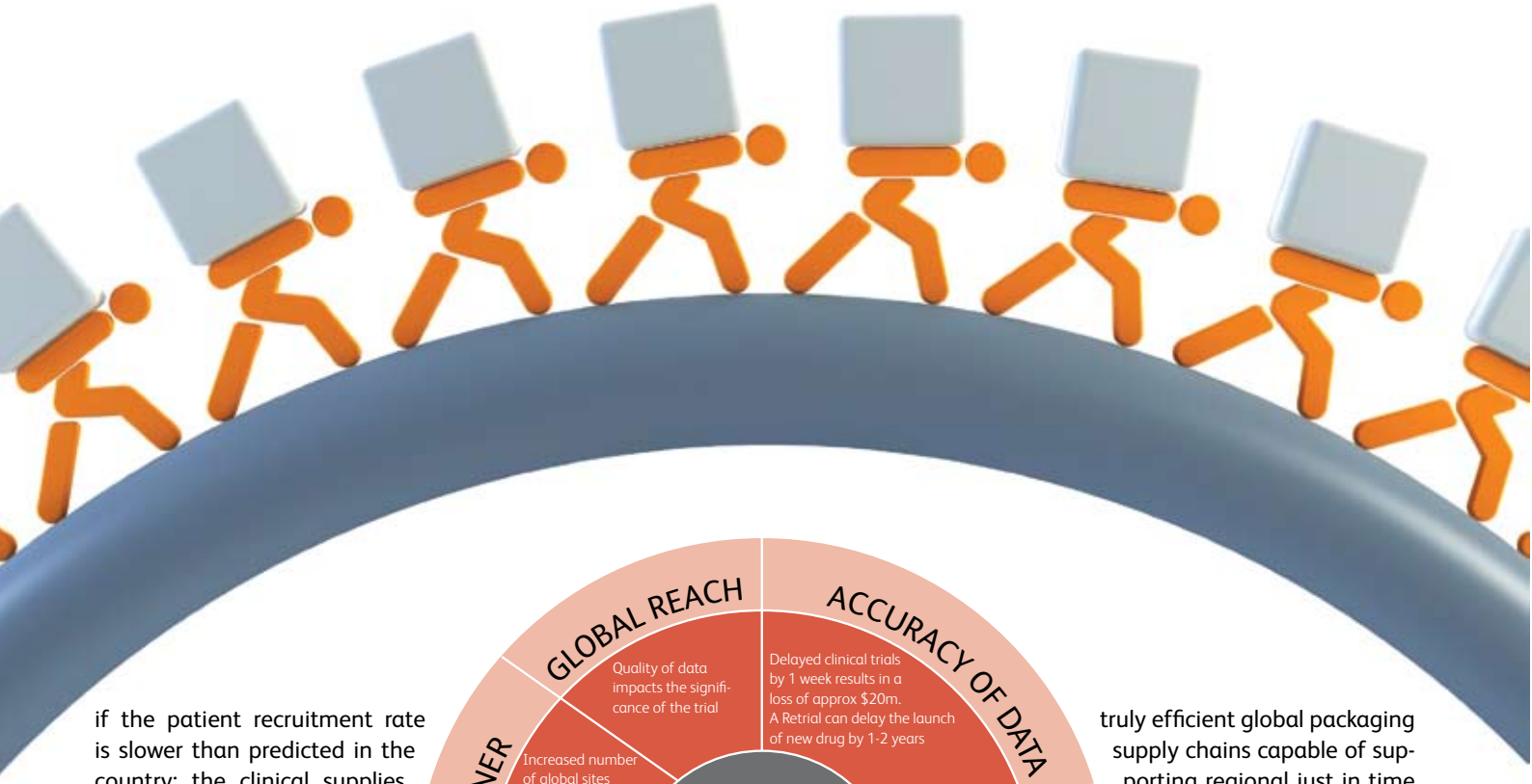
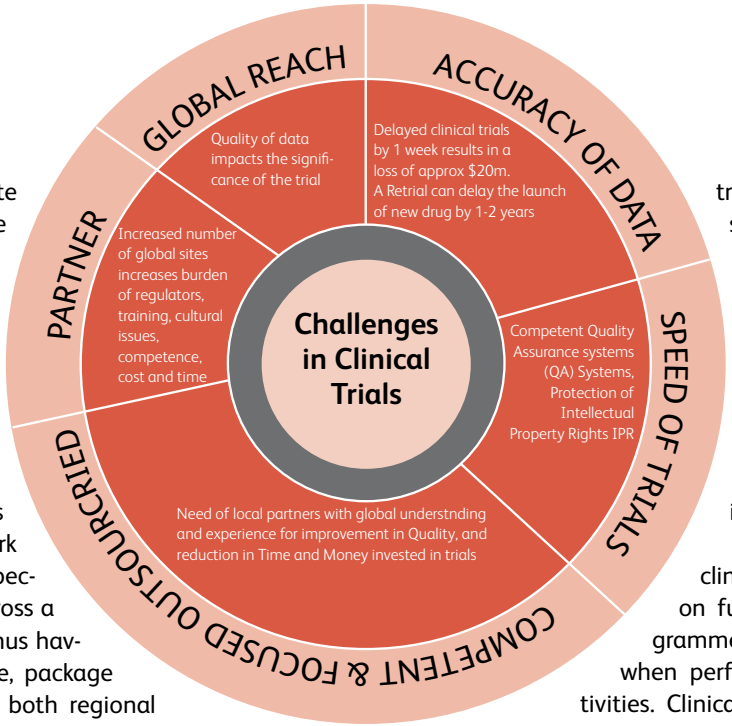




if the patient recruitment rate is slower than predicted in the country; the clinical supplies will then have to be exported following importation into the country. This import/export restriction within one country is extremely challenging.

In order to evaluate the optimal supply chain, with the greatest flexibility, the groups supporting the supplies work need to perform a similar spectrum of service capabilities across a global footprint of facilities. Thus having the ability to manufacture, package and label clinical supplies for both regional and global study supplies removes constraints in the supply chain.

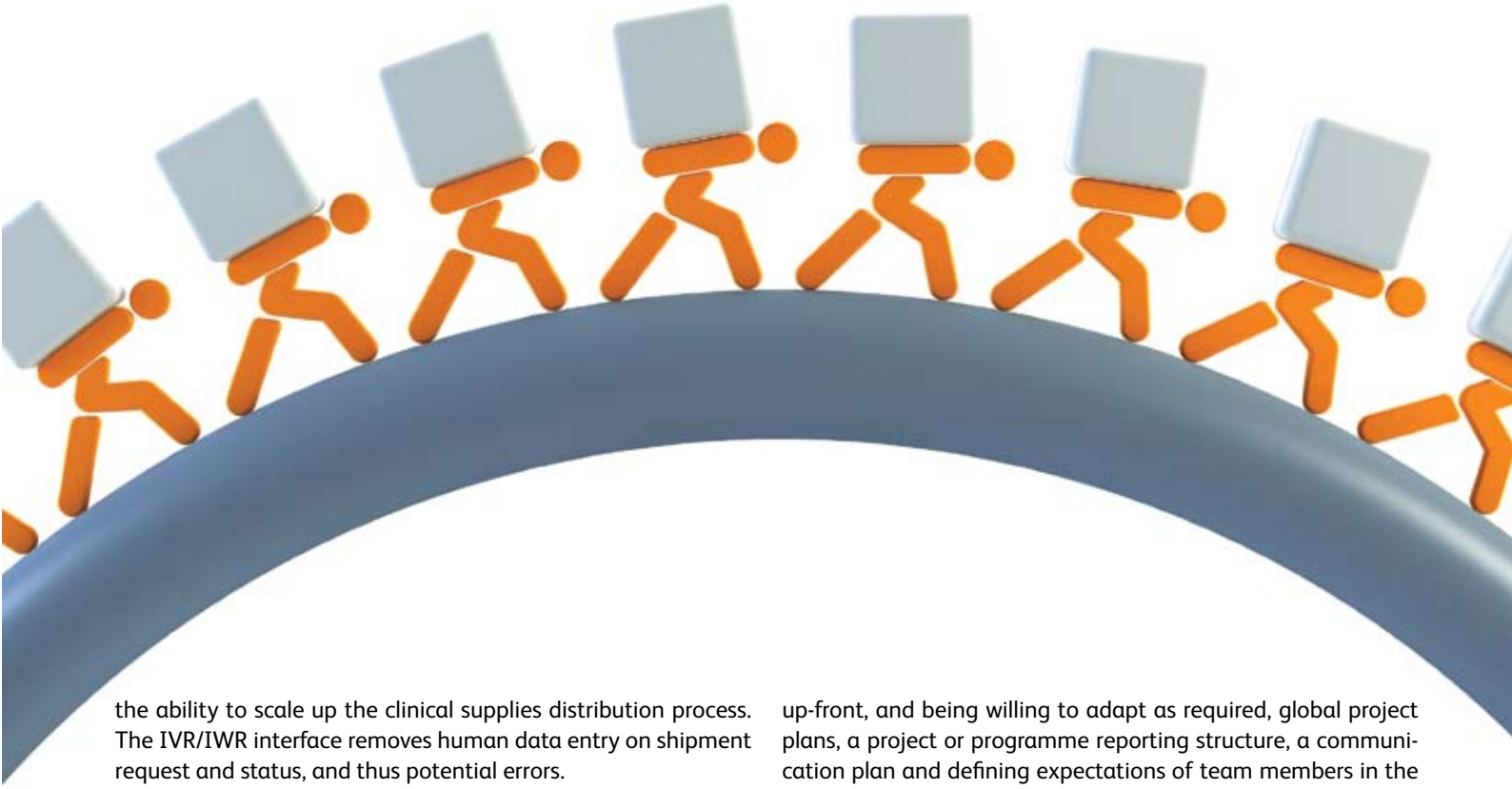
The clinical supplies group will also need a global project plan, reporting tools, a communication plan and infrastructure to report the status of the study or programme from a clinical supplies perspective to the rest of the trial team.

Global approaches to primary and secondary packaging can assist with both optimising and adding flexibility into supply chains. Currently the clinical supplies industry is focused on automation and the adoption of standardisation of approach to the equipment and components being used. This also means the third party suppliers used between facilities need to be global. The risk with pack standardisation is that more complex packaging solutions are overlooked and patient compliance levels compromised.

In the future it has been speculated that there will be pressure for just in time packaging/labelling and release. As drug cost grows, the amount of drug available is lower, and there is increased pressure to reduce the amount of unused drug currently being packed. Added to this, the number of compounds in the clinic requiring cold chain storage and distribution and studies using adaptive trial designs are increasing. With these studies and their inherent challenges, the only way to assemble truly efficient global packaging supply chains capable of supporting regional just in time packaging, labelling, release and distribution to clinical sites is the harmonisation of processes and service delivery. There will be a greater need to integrate more regional packaging facilities into the supply chain.

It will be essential for the clinical supplies group to work on fully integrated software programmes to offer parity of approach when performing the just in time activities. Clinical supplies groups today use proprietary enterprise/manufacturing resource planning (ERP, MRP), label design and print systems, or in-house developed software, or a mixture of both. Whatever the combination, there will be a greater need for integration in global control and reporting systems. This ensures that the clinical trial materials are packaged, labelled and released correctly according to the randomisation schedule and regulatory requirements for the material, regardless of the location.

Harmonised informatics platforms also allow for a consistent approach to unique pack identification in the global inventory system, by barcodes, RFID or proprietary tagging technologies. These all enhance accuracy in the clinical supplies inventory, distribution set-up and execution of the clinical supplies pick and pack shipment process. These systems also allow wider team access, via secure portals, to blinded and un-blinded inventory reports, warehouse storage conditions, pending shipment status, shipment history and in-transit track and trace. Adding the functionality of clinical supplies returns to the informatics platform allows “cradle to grave” reporting capability for the clinical supplies. The ability to integrate these systems with interactive voice/web response (IVR/IWR) platforms, via a File Transfer Protocol (FTP) site or similar electronic file-sharing interface, has become commonplace. This interface is now seen as essential to



the ability to scale up the clinical supplies distribution process. The IVR/IWR interface removes human data entry on shipment request and status, and thus potential errors.

When shipping, USB-enabled temperature monitoring devices for both cold and increasingly controlled ambient supplies can be used. The electronic interface also allows temperature traces to be associated to the specific shipments and kits.

A further benefit in Europe to utilising and closely interfacing clinical supplies with the IVR/IWR platform is the potential to move to expiry date-free labelling. This has been slow to gather momentum, but in the future, should the adoption of electronic patient diaries take predominance, it is another area that the supplies can interface in the supply chain. The use of smartphones and personal digital assistant(PDAs) and the integration of supplies into electronic-patient reported outcomes (e-PRO), that can read dispensed Investigational Medicinal Products (IMP) kit labels in patients' hands, will allow better control of expiry date-free IMP and offer the potential to assist with compliance and pharmacovigilance monitoring.

The industry standard approach to measuring and managing the performance of a supply chain solution is the adoption of metrics and key performance indicators (KPIs). Increasingly service level agreements are placed on the clinical supplies groups by the clinical teams/sponsors. Supplies groups must be mindful that these service level agreements are also built into the critical vendors they use such as couriers and depots. The simplest way to cover this is by measuring and managing these service providers in the supply chain to the same KPIs. On-time release of kits, on-time delivery of IMP to site, and minimising temperature excursions in transit are really all that matter, but right first time documentation and other quality-related non-conformances/complaints/corrective and preventative action (CAPA) close outs are the indicators of quality and efficiency of a clinical supplies supply chain. These KPIs allow clinical and supplies teams, along with the sponsor, to measure and manage elements of the supply chain that affect the study objectives (on time, on budget, and with a high level of quality built into the processes).

Good project and programme management can significantly enhance the success of a clinical supplies supply chain. Agreeing up-front, and being willing to adapt as required, global project plans, a project or programme reporting structure, a communication plan and defining expectations of team members in the supply chain, are essential to clearly defining roles and responsibilities. Periodical status updates from across the supply chain back to the project management team ensure that everything is in control, or establish if certain elements of the supply chain need more support to overcome a challenge.

The M&A models, discussed in the first part of this review, further highlight the differing needs for scale and approach to clinical supplies. The smaller development groups and the large pharma model have different demands for their ideal clinical packaging supply chains.

The holy grail of clinical supplies services is to develop a cultural mindset to work on supply chains that are nimble, responsive and innovative, which rapidly accommodates Phase I clinical trials packaging, whilst also having the global presence, processes and capacity for managing multiple Phase III trial packaging needs.

Building successful supply chain solutions in clinical trial supplies needs careful planning. When considering clinical supplies activities the proposed supply chain must be focused on achieving a flexible model to allow for unforeseen changes to the study or programme.

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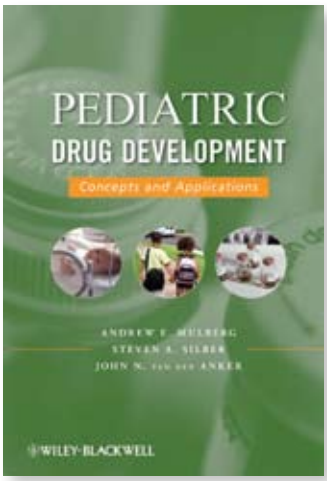
Pediatric Drug Development
Concepts and Applications

Andrew E Mulberg, Steven A Silber, and John N van den Anker



Historically, many medical products, including pharmaceuticals, have not been tested in children. There has been resistance to do so for many reasons. The author of Chapter 3 in this outstanding book put pediatric clinical trials into context very well: "Using children as the subjects of scientific study is a topic that never fails to stimulate debate, whether broached in scientific circles, in the ethics domain, or in the public media. No-one questions the need or desire to know more about conditions affecting the health and well-being of children, whether from the physiological, psychological, or pathological vantage point. And yet, even with everyone in agreement on this fundamental point, the avenue forward soon splits into many different paths, some less well traveled than others, some highly risky if not treacherous, and most seemingly fraught with obstacles at every turn."[1]

With regard to pharmacotherapy, the US Food and Drug Administration's (FDA's) Office of Pediatric Therapeutics plays a major oversight role. It addresses ethical issues and protects children who participate in clinical trials, but also works towards "timely access to medical products proven to be safe and effective for children."[2]

Physiological processes that influence pharmacokinetic variables in the infant change significantly in the first years of life, particularly during the first few months. Metabolism is quite different in early neonatal life than later, with different enzymatic systems approaching adult characteristics at different rates. A similar problem can arise to that often seen in elderly patients, or others with compromised metabolism and/or elimination: unless drug doses are tailored appropriately, higher than intended plasma concentrations are likely, increasing the risk of adverse drug reactions.

As hinted at by the quote at the beginning of this review, including children in clinical trials is a topic that brings forth a wealth of emotion. Is it not our ethical and moral duty to protect our children from any dangers in life, including those that may be present when children are included as experimental subjects in clinical trials of pharmaceutical products? Yes, it is indeed our duty to protect our children. However, there is a flip side to this coin. As the FDA has commented, "Children's bodies are not just small versions of adult bodies. Modifying the adult dose of a medicine might not result in the safe and effective treatment of a child."[3] In a very real sense, any time a child is prescribed a drug that has not been tested in pediatric clinical trials, that child is participating in an "N of 1" clinical experiment. That is, we truly do not have a sound knowledge base to predict with any degree of certainty what the child's response will be. As others have argued (convincingly so to this author), it is scientifically, medically, and ethically more justifiable to conduct rigorous and rigorously monitored clinical trials that will provide a sound knowledge base for pediatric pharmacotherapy than to continue to experiment on every child who receives a modified dose of an adult-tested drug on a one-by-one basis.

In March 2004 the FDA released its Critical Path Report, and subsequently released its Critical Path Opportunities List in March 2006.[3] This list, regarded as an initial summary of key scientific opportunities to improve product development, identified targeted research that the FDA believed, if pursued, "will increase efficiency, predictability, and productivity in the development of new medical products." Included among the six topics forming the basis for the opportunities list was pediatrics.

Pediatric Drug Development is a comprehensive work that will be of interest to a very diverse set of readers. It takes a global perspective in both senses of the word, covering a very wide range of topics and addressing regulatory guidances in all three of the major ICH regions - Europe, Japan, and the United States. The editors are to be congratulated for taking the lead in bringing this material to the forefront of drug development at an auspicious time as widespread interest in their topic quite rightly grows, and for selecting appropriate authors to further their very important cause.

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ISBN: 978-0-470-16929-2

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www.healthnetworkcommunications.com/2010/exploreusa

Achieving Operational Efficiency in Clinical Trials 2010
Date: 6 - 7 October 2010
Brussels, Belgium
www.arena-international.com/pharma/clinops

8th Annual Clinical Trial Supply East Coast 2010
Date: 20 – 21 October 2010
Philadelphia, PA
www.clinicaltrialsevents.com/east-coast2010

Canadian Association of Radiation Oncology Annual Scientific Meeting
Date: 22-25 September 2010
Hyatt Regency Hotel, Vancouver, BC
www.ecco-org.eu/Conferences-and-Events/Calendar-of-events

10th International Conference on Cancer-Induced Bone Disease
Date: 22 - 25 September 2010
Sheffield, UK
www.cancerandbonesociety.org

5th Croatian Congress on Alzheimer's Disease
Date: 22 - 25 September 2010
Zadar, Croatia
www.alzheimer2010.com/en/index.php

9th annual Partnership In Clinical Trials
Date: 17-18 November 2010
Reed Messe Wien Congress Center, Vienna, Austria
www.ct-partnerships.com

Progress in Paediatric Neurology research conference Leuven, Belgium, October 1-2, 2010
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Advancing Clinical Trials in CNS
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