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Navigating to China for global clinical trials

If necessity is the mother of invention then it shouldn't come as a big surprise that China, the world's largest and most populous country inhabited by over 1.3 billion people, possesses an enormous driver for healthcare. Inevitably, with its vast potential for clinical research and development this huge country attracts global pharma companies and CROs to do business.

It's not merely the unmet demand for Western medicines but also preventive treatments, including vaccines, where the greatest scope exists for a collaborative effort. China recently introduced a major new commercialisation policy that includes a budget to support research in the country's vaccine industry. The policy, together with the earlier dissolution of the state monopoly on purchasing vaccines, will make the biotech sector in China more competitive and allow entry of foreign vaccine developers. This could put new vaccines onto the Chinese market if vaccine companies invest in research and introduce marketing strategies that raise awareness among the general population of the need for vaccines.

Probably the biggest challenge for prevention and treatment is with HIV/AIDS. According to HIV Vaccine Trials Network, China's first AIDS outbreak was not reported until 1989, in Yunnan province near China's southwest border. Today, about 650,000 people in China are living with HIV/AIDS. Although a small fraction of China's population, the sheer number of people at risk is daunting. Yunnan, with 44 million inhabitants, remains the most concentrated region, with about 80,000 people infected with HIV, a half of them involving intravenous drug users who spread the disease by sharing needles. Other areas of HIV/AIDS concentration are in Henan, central China, Xinjiang in northwest, Guangxi and Guangdong in the south.

Among companies with an interest in HIV, Avexa Limited entered into a licensing agreement with the Shanghai Institute of Organic Chemistry (SIOC) to develop one of Avexa's HIV integrase inhibitor series. SIOC takes responsibility for future development costs of the program in China and will pay Avexa 50% of any net commercialisation revenues. Avexa retains all development and marketing rights for the program outside of China.

Among major CROs, PPD opened its first office in China in 2003. Simon Britton, PPD's vice president of clinical development for Asia Pacific sees the vaccines market as one of the fastest growing segments in the industry. In China the clinical trial market is growing at about 20% each year.

In April 2010, PPD opened a vaccine clinical research centre at the Taizhou China Medical City in order to provide clinical monitoring services to global and local biopharmaceutical companies seeking to develop vaccines in China. In China, vaccine studies are carried out by the Chinese Center for Disease Control and Prevention instead of them being done in Phase I clinics or by investigators at hospitals. The studies require thousands of patients for enrollment, compared to hundreds for studies conducted in other countries. Even so, China has a short recruitment period for vaccine trials so they are completed a lot quicker.

In this issue of JCS, there's a feature article about clinical trials in China (see pp 110) by Harriet King, Marketing Executive of Biocair International, giving an insight into the conduct of clinical trials in Asia.

Looking ahead Terrapinn is organizing its World PharmaTrials Asia 2010 4-day event, from 13-16 September 2010 at Gran Melia, Shanghai, China. Day two of the conference will deal with flu vaccine trials responding to pandemic threats and the recruitment of patients for vaccine trials.

Further details from Terrapinn: http://www.terrapinn.com/2010/pharmatrialscn/index.stm or contact Fiona Ho, by email: world.events@terrapinn.com or phone: +65 6322 2320 / +65 9794 9527.

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Adaptive Design Clinical Studies for Human Drugs and Biological Products

In the realm of clinical research and development, the use of adaptive design methods allows for modifications to be made to aspects of ongoing studies. To assist sponsors in planning and conducting adaptive design investigations, the US Food and Drug Administration (FDA) published the Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics(1) in February 2010.

The FDA explains that there is considerable interest in the possibility to design clinical trials with adaptive features that may make the studies more efficient (e.g., shorter duration, fewer patients), more likely to demonstrate a treatment effect if one exists, or more informative on the effect (e.g., broader dose-response findings). Adaptive features are changes in the study design or analyses based on assessment of the accumulated data at an interim point in the trial. Examples of changes are modifications to the randomisation procedure, the study sample size, or the primary endpoint.

Of chief focus in the draft guidance are adequate and well-controlled (A&WC) studies intended to provide substantial evidence of efficacy required by law, to support a conclusion that a drug or biological product is effective. Characteristics of A&WC studies are detailed in 21 Code of Federal Regulations (CFR) Part 314.126.(2)

While adaptive design methods present the possibility of several benefits, there are some caveats. One issue is the potential to increase the chance of false positive conclusions (increased Type I error rate). Adaptive designs often involve choices made from multiple candidates (doses, endpoints, etc), creating numerous chances to succeed in showing a treatment effect with a greater likelihood of doing so compared to when choices are lacking. It is cautioned that the bias inherent in such multiplicity may be difficult to understand and account for statistically in complex cases. Central to reducing or eliminating bias risk is to have adaptations rely only on blinded analyses, and to ensure that blinding is strictly maintained.

Types of generally well-understood adaptive designs with valid implementation approaches are outlined in the draft guidance. For example, some adaptive methods use a group sequential design. (3) In this type of design, unblinded interim analyses of accruing study data are used in a planned and confidential manner (i.e., by a data monitoring committee [DMC](4)) that controls Type I error and maintains study integrity.

Several components are required by the FDA for an adaptive design A&WC study protocol. These items are: 1) a summary of the relevant information about the drug product; 2) a complete description of all the objectives and design features of the adaptive design; 3) a summary of each adaptation and its impact on critical statistical issues (e.g., hypotheses tested, Type I errors); 4) computer simulations intended to characterise and quantify the level of statistical uncertainty in each adaptation and its impact on the Type I error, study power, or bias; 5) full detail of the analytic derivations, if appropriate; and 6) the composition, written charter, and operating procedures for the personnel assigned responsibility for carrying out the interim analyses, adaptation selection, and any other forms of study monitoring. ●

References:

1. US Food and Drug Administration. Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, February 2010, Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

2. 21 Code of Federal Regulations, Part 314.126. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126

3. US Food and Drug Administration. Guidance for Industry: E9 Statistical Principles for Clinical Trials, September 1998. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf

4. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf

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Caribbean Watch part 3

Building a clinical research practice in an emerging market warrants exploration. One question that comes to mind is, if you build it, will they come? The answer to that question rings familiar as in one classic American movie, Field of Dreams. Yes, "if you build it, they will come", and in Field of Dreams, they came, the success was extraordinary, and so it went.

With the Caribbean being an emerging market, one will wonder about the risks and benefits involved with conducting a successful clinical trial in this market. So, to further explore this, let's examine what the region offers.

The demographics. The majority of the population is of African descent and is described as Afro-Caribbean. Other populations represented demographically include Hispanic, Anglo-Saxon and Asian. Each of these groups exhibit their own ethnocentricities that makes them distinct in their existence, culture, diet and lifestyle being the major factors. Historically, clinical trials have been under-represented by persons of African descent, including the Afro-American and Afro-Caribbean sub-groups. There is a co-morbidity that exists in the Afro- (American or Caribbean) demographic group that raises the question of whether multi-treatment meds are appropriate? Is the recommended dose appropriate?

Data and statistics from the Pan-American Health Organization, reports that diabetes, obesity, hypertension and cholesterol are leading diseases that impact the mortality of this region. Hence, clinical trials focused in these areas will surely recruit well. Historical data tells us that patient screening and recruitment, subject compliance, and retention are all remarkable.

Due to the warm, moist climate in the Caribbean region, there are some concerns for climate-related diseases and conditions.

Research into resistant fungal infections, anti-infective research and tropical medicine, to name a few other therapeutic areas, all have a place in this region.

When considering study site locations and commutability for monitoring, convenience and expense factors, the Caribbean region offers a convenient commute from most major cities, including New York, Miami, North Carolina and Atlanta in the US, and London, Manchester, Edinburgh, Dublin and Amsterdam in the UK.

As this region continues to develop as an emerging market for clinical trials, providing experienced investigators and study teams is ongoing. Key individuals have been identified to create these study teams, trained in Good Clinical Practice and ICH Guidelines. Caribbean Clinical Research Associates, LLC (based in St. Kitts and Nevis) has for the past five years been forming ties with sponsors and CROs interested in conducting clinical research trials in the region. Investigator-initiated clinical trials have been submitted to major pharma sponsors and are awaiting response. A relationship has been established with Diversified Healthcare Solutions, Inc in St. Kitts, which is involved in psychiatry, in addition to the other therapeutic areas mentioned. Eureka Health Services Ltd, in Nevis is involved with a private practice focusing on general medicine and diabetes care. Other physicians and study team members are trained and available for a variety of projects.

St. Kitts and Nevis, one of the smaller of the Caribbean islands, has a proven track record in conducting clinical trials. The most

Submission of relevant documents to CRO/SMO

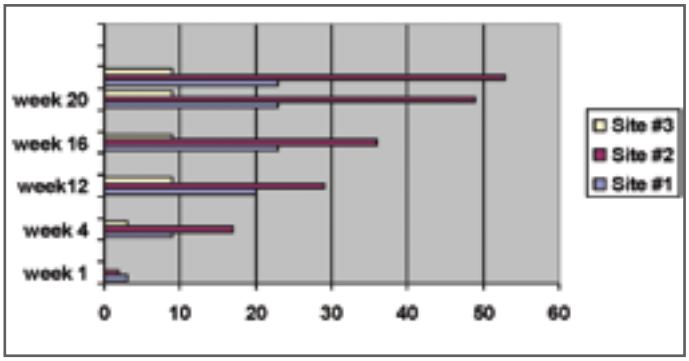
↓

Preparation of local Ministry of Health/Ethics Committee application and submission of relevant documents (one week)

↓

Response from local MOH/EC (response time varies; usually three days for a verbal response, total 7-10 days for document issue)

Submit document to sponsor/central IRB (response time varies) ↔ Apply for duty concession on study supplies and approval of investigative material to clear customs (one week)



recently completed trial, in the area of tinea pedis, proved a significant response in subject recruitment and retention. The graph below represents the enrolment trend for that clinical trial.

Local Regulatory Requirements and Institutional Review Board. Regulatory requirements in an emerging region can at times be non-existent. In the Caribbean region, government permission usually comes from the local Ministry of Health. Institutional Review Boards located in this region are usually affiliated with a local medical university. You may find that the larger island nations may have an Ethics Committee in place which will provide the necessary approvals

Steps to Study Approval in Caribbean Region to conduct the clinical trial within ICH-GCP guidelines. It has been experienced that the response time from the Ministries of Health varies, with usually some verbal indication in days and a follow-up document acknowledging the intent of the research and approval to move forward. A central IRB would request a document from the local regulatory agencies to that effect. Below are the steps to study approval and initiation.

Conclusion

With several island nations to choose from, the Caribbean region is a valuable emerging region for the conduct of clinical research trials, with larger demographic locales and smaller simpler locales, with local Ministries of Health reviewing and giving approval in reasonable timelines. These governing bodies are recognising the importance of participating in clinical research studies, and have expressed an interest in supporting these projects. The islands offer a convenient commute for study monitoring, personnel trained and experienced in ICH GCP guidelines, strong recruitment, enrolment and subject retention numbers, and a variety of therapeutic areas. For these reasons, this region has great potential.

Francine Hakim, BS, CCRA is the president and founder of Caribbean Clinical Research Associates, LLC, a consortium of physicians and health care professionals conducting clinical trials serving the Caribbean. CCRA assists with logistics for timely approvals and clean study conduct. CCRA keeps a pulse on the research activities and thought leaders of the region. Its principal, Ms Hakim has 15 years experience in the pharmaceutical research industry in business development, project management, full scope of site monitoring, auditing, training and lecturing. . If you are interested in learning how your next trial will be conducted in the Caribbean.
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New Regulations in Clinical Trials in India

The market value of clinical trial research outsourced to India, which grew by 65 % in 2006 alone, is expected to climb to $1.5-2 billion by 2010 from the present estimated value of $300 million. The reason the business is growing so rapidly is that the pharmaceutical industry is required by government regulations to conduct human trials before marketing new drugs.

As the US and European drug giants are increasingly outsourcing their clinical testing to the rapidly developing economies like China, India and Africa, the Indian government is planning to enact new regulations to control drug trials in the country by establishing a Central Drug Authority that will keep a watch over the activities, and ensure the ethics of the trials being conducted in India, in addition to providing additional regulatory support.

Regulations pertaining to clinical trials in India are governed by Schedule "Y" of the Drug and Cosmetic Act. It deals with regulations relating to clinical trial requirements for the import and manufacture, and obtaining marketing approval for a new drug in India. The procedure for applying for marketing approval depends on the status of the new drug, which can be broadly classified into three categories: new drug substances discovered that are already approved/marketed in other countries; new drug substances discovered that are not approved/marketed in other countries; and new drug substances discovered in India. This article will give an understanding of the areas where there has been a change.

Clinical trials

As compared to the current Schedule Y, which has narrow and restrictive definitions of clinical trial phases, the new draft provides pragmatic definitions for Phases I to IV. The definitions and guidelines for clinical trial phases are broad and rational, and the earlier restrictions on number patients and centres in early phases have been removed, allowing the sponsor freedom to decide these in relation to protocol requirements. The phase lag requirements have given way to acceptance of concurrent Phases II and III as part of global clinical trials (CTs). However, Phase I for a new foreign drug will not be permitted India.

A notable feature is flexibility in data requirements for new drugs for life-threatening/ serious conditions or diseases of relevance to India. There is also a new classification of Fixed Dose Combinations for clinical studies.

One of the issues for global CTs was dual permission - from DCGI office and DGFT - for export of trial samples to a central laboratory abroad. Now the sponsor is likely to obtain this permission through the DCGI office. There is a special focus on certain vulnerable populations eg. paediatrics, geriatrics and pregnancy. The sponsor may be asked to generate CT data as part of an investigational new drug application, if the indication is relevant to any of these special populations.

Ethics Committee (EC) and Informed Consent: one of the lacunae in complying with GCP was composition and functioning of the EC. The revised Schedule Y devotes significant attention to roles and responsibilities of the EC. It also describes composition of the EC as per the ICMR guidelines, and provides formats for the approval of EC letter.

The revised Schedule Y stipulates that EC approval of protocol / informed consent form (ICF) is essential, and the EC approval should be notified to DCGI prior to initiation of the clinical trial. It also allows trial sites without EC to accept the approval granted to protocol by the EC of another site or Independent EC, provided the approving EC is willing to accept their responsibilities for the site without an EC.

By including Independent ECs, this provision also provides for regulatory recognition of Independent ECs. An EC for paediatric trials has to include members knowledgeable about paediatric, ethical, clinical and psychosocial issues. The general requirements of ICF and special situations (those who are illiterate or unable to give consent) are described. There will be a new requirement for mature minors and adolescents to sign an assent form.

There are also appendices detailing a checklist for informed consent documents, and the format for the informed consent form. The format specifies that besides the patient's signature at the end of the form, his initials are also required on all five consent clauses.

Guidelines for Investigator: the investigator should have appropriate qualifications and experience, as well as access to relevant investigational and treatment facilities, and will be responsible for the conduct of the trial according to protocol and GCP. Besides, he has to sign an undertaking which demands several commitments. Some of the commitments are: -

- Ensure that study will not begin until EC/ DCGI have given approval
- Agree to adhere to protocol and provide personal supervision Ensure requirements of IC and EC review are met
- Agree to report any Adverse Drug Event to sponsor
- Agree to maintenance of records and availability for audits / sponsor inspection / EC and DCGI
- Ensure that all associates, colleagues and employees are suitably qualified and experienced, and are aware of their obligations
- Consent to cooperation in audits
- Ensure prompt report to EC about changes and unanticipated problems
- Agree to confidentiality of data and patients
- Accept compliance with all other obligations of clinical investigators

Responsibility of Sponsor: the sponsor will be responsible for implementing and maintaining quality assurance to ensure compliance to GCP guidelines of CDSCO. The sponsor will have to submit status reports at prescribed intervals, and also inform DCGI of the reasons for premature termination. The period for reporting Serious Adverse Events is now defined. A Serious Adverse Event has to be communicated promptly (within 14 calendar days) to DCGI and other investigators.

Checklists and formats: There are several appendices which cover some critical data requirements, formats and checklists. These are:

- Data for submission along with clinical trial application
- Animal pharmacology
- Animal toxicology
- Undertaking by investigator
- Ethics committee and format of EC approval
- Checklist of contents and format for ICF
- Structure and content of report

- Fixed dose combinations
- Study conditions for drug storage
- Content of protocol.

Overall Perspective: the changes in clinical trial definition and acceptance of multi-national concurrent Phase II and III will rationalise regulatory guidelines for the integration of India in global clinical development.

The focus on ethics committee composition and function will go a long way towards bringing uniformity in EC function and improving GCP compliance. The additional five signatures on the ICF will be inconvenient for both the patient and the investigator. The compliance undertaking by the investigator is unlikely to find favour with the sponsor. It is likely to lead to conflict between the sponsor and investigator, and may dampen the enthusiasm of a good investigator. As there are differences between Indian GCP and ICH-GCP guidelines, the audit of an Indian trial will be a challenging task for the foreign sponsor's auditors and the Indian subsidiary.

GCP is considered a shared responsibility between sponsor, investigator, regulatory authority and ethics committee. Until now, there was no regulatory enforcement of GCP compliance. In the absence of regulatory support, the onus of GCP compliance, to a large extent, fell on the sponsors with some support from the investigators.

Conclusion:

As things stand today, it is a myth that CROs are still in their infancy in India. The total market value of clinical research performed in India in 2001-02 was about $70-80 million. The firm increase in CRO activities can be attributed to large subject pools in most major therapeutic areas, improved medical infrastructure, and increased awareness of the ICH Guideline for Good Clinical Practice and formation of specialised researchers, and last but not least the globalisation of the pharma industry. ●

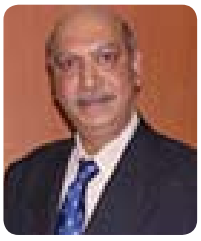
References:

1. US Food and Drug Administration. Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, February 2010, Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

2. 21 Code of Federal Regulations, Part 314.126. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126

3. US Food and Drug Administration. Guidance for Industry: E9 Statistical Principles for Clinical Trials, September 1998. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf

4. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf



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Cardiovascular Safety Watch column

The terms non-clinical (or pre-clinical) development and clinical development have historically reflected a dichotomy between these components of new drug development. However, more recently, it has become widely acknowledged that they are much better conceptualised as stages in a continuum of development activities that are beneficially integrated to the greatest extent possible. This continuum can be thought of as lifecycle drug development, in which *in silico* modelling and drug design, non-clinical development (*in vitro, ex vivo,* and *in vivo*), preapproval clinical development, postmarketing clinical trials and postmarketing surveillance combine in an ideally seamless manner to effect safe and effective pharmacotherapy.

Much attention is now focused on how best to predict adverse events in clinical trials from data collected in non-clinical development programmes. Despite acknowledgement of the importance of integrated risk profiles, however, it remains a challenge to predict human adverse events from non-clinical data with a high degree of certainty. As Greaves noted, "The outstanding difficulty in this area of drug development remains the prediction of likely adverse effects in patients based on findings in laboratory animals." [1]

Within the domain of cardiovascular safety, it is of considerable interest to determine how reliably and accurately information from non-clinical investigations predicts the degree of proarrhythmic liability that will be seen when an investigation drug is administered to human subjects in preapproval clinical trials. Classical non-clinical assays include the in vitro hERG channel assay (designed to evaluate the degree to which a compound alters the repolarising potassium ionic current flowing through this channel in the plasma membranes of cardiac myocytes), and the in vivo QT assay (designed to assess the degree to which the investigational drug alters the QT interval seen on the surface ECG). [2] However, more comprehensive and sophisticated assays are being included in the creation of overall cardiotoxicity predictive profiles. This was reflected at the recent World Pharmaceutical Congress (Philadelphia, June 15-17th). This meeting had several tracks, including one entitled Monitoring Cardiovascular Toxicity and Drug Safety. The leading session in this track was entitled "Translating Pre-clinical

Predictions to Clinical Safety", and presentations included "Pre-Clinical Cardiac Safety: Moving Ahead of hERG", "Enriched Human Cardiomyocytes from Embryonic Stem Cells for Drug Discovery and Safety Pharmacology", and "High Content Cardiotoxicity Profiling with Engineered Heart Tissues: Mitochondrial Toxicity and Genomic Influences."

When moving from in vitro to in vivo intact animal models, tissue assays can be useful bridging studies. The most established is the Purkinje fibre assay, in which action potentials are measured in fibres isolated from the heart using conventional intracellular recording. While both canine and rabbit Purkinje fibres have been employed in this context, the rabbit assay may be preferable, since in direct comparison with the canine assay, it has been found to have greater sensitivity and specificity. Guinea-pig isolated myocytes appear more sensitive for detecting action potential prolongation with compounds inhibiting multiple ion channels. The arterially perfused rabbit left ventricular wedge preparation is also of interest. Wang et al. [3] recently reviewed the current and prospective role of this assay in the assessment of drug-induced proarrhythmias, and reported that, in blinded validation studies, the assay predicts drug-induced TdP with an extremely high sensitivity and specificity.

One professional society that exemplifies an integrated approach to drug safety is the Safety Pharmacology Society. As the term safety pharmacology reflects, the origins of this Society are firmly founded in non-clinical investigations. However, as will be seen in presentations and discussions to be held at the Society's 10th Annual Meeting to be held in Boston this coming September (see http://www.safetypharmacology.org/am2010/index.asp), the translation from non-clinical to clinical adverse drug responses is now an important part of the meeting's agenda.

As a concluding comment, it is worth noting an observation from Turner and Durham: "Many professionals bring diverse sets of skills to the domain of drug safety. The more integrated the efforts of everyone concerned, the better all patients will be served." [4].

References:

1. Greaves P, 2007, Histopathology of preclinical toxicity studies, 3rd Edition. New York: Academic Press/Elsevier.

2. ICH Guideline S7B, 2005, The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals. (http://www.ich.org/LOB/media/MEDIA2192.pdf)

3. Wang D, Patel C, Cui C, Yan G-X, 2008, Preclinical assessment of drug-induced proarrhythmias: Role of the arterially perfused rabbit left ventricular wedge preparation. Pharmacology and Therapeutics. 2008:119;141-151.

4. Turner JR, Durham TA, 2009, Integrated cardiac safety: Assessment methodologies for noncardiac drugs in discovery, development, and postmarketing surveillance. Hoboken, NJ: John Wiley & Sons, p. 396.

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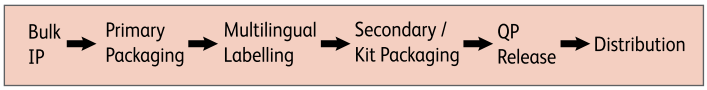
Benefits of Just-In-Time (JIT) Preparation of Investigational Products (IP)

Costs and performance of multicentre, multinational clinical studies are dependent, among other things, on the anticipation of patient recruitment per site and per country, and the total amount of study medication which will be needed throughout the study. Experience shows that the original planning often does not match the reality, either due to a surplus of medication being produced on the one hand, or frequent additional supplies being necessary on the other, for example due to additional countries being added to the study. A rather simple process may help to reduce expensive surplus supplies of study medication and allow adaptive planning from the beginning of the study: Just-In-Time (JIT) packaging and labelling.

1. Typical IP manufacturing flow:

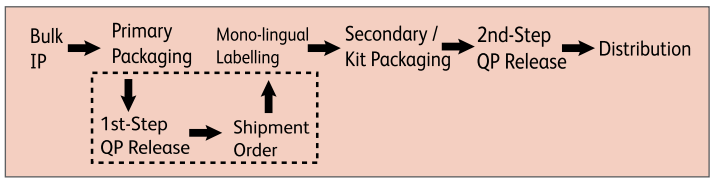
The typical flow of IP manufacture requires a thorough planning of amounts, sites and countries, which can be challenging, especially when double-blind crossover designs are applied.

The anticipated amount of study medication packs or patient kits is prepared before the start of the study, and later modifications like addition of countries or change of dosages is no longer possible, or is only possible by considerable additional work.



2. Alternative: JIT packaging and labelling:

JIT packaging and labelling might be an interesting alternative to overcome restrictions caused by, for example, IPs which are limited in their availability and/or very expensive.



Explanations:

- The 1st-step QP release is done against the CTA application and the PSF as usual.
- The shipment order may be country-, centre- and investigator-specific.
- Labelling and secondary packaging / kit packaging is done individually for a specific shipment order.
- The 2nd-step QP release is done against the individual shipment order (check for correct labelling and packaging only).

3. Advantages of JIT packaging and labelling

- One batch of primarily packaged IP can be used for several studies at the same time.
- Several batches of bulk IP can be used dependent on their availability (sequential preparation).
- Only study medication already ordered will be prepared.
- Cheap and rapidly-available single-panel labels can be used.
- Label phrases and design may be selected and approved independently and individually per country.
- Label contents may be modified during the study according to adaptations becoming necessary (e.g. use-by date).
- Centre activation of each country can occur independently from the other countries.
- Dose titration can be done during the study without wasting labelled medication.
- Re-supply only limited by the stock of primarily packaged IP.

4. Additional work caused by JIT packaging and labelling

- Each shipment order requires a separate labelling and packaging exercise
- Each shipment order requires a separate, reduced QP release

5. Conclusion

JIT packaging and labelling is considered to be an attractive alternative for studies with the following characteristics:

- Study to start in each country as soon as the national CTA has been received.
- Limited availability of study medication.
- Study medication being very expensive.
- Initial dose titration phase with high variability of final individual doses.
- Additional countries to be included after start of studies which have been supplied with multilingual labelled study medication.
- The manufacturer's QA structure allows for frequent 2nd-step QP release.

Dr. Claudio Alexander Lorck, has over 21 years experience in the fields of Quality Control and Clinical Trial Materials Management. Having started his pharmaceutical career at Fujisawa Deutschland GmbH, Claudio now heads the business unit "Clinical Trial Materials" of Temmler Werke GmbH.
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Interview: Saudi Food and Drug Administration

Dr. Al-Rohaimi is the Director of Research and Publishing Drug Sector of the Saudi FDA. He graduated as a dentist with a master's degree in dental surgery, his interest in drug discovery started with his pharmacology studies as he was awarded PHD in pharmacology. Dr Al-Roheimi started his career 14 years back with teaching posts in prestigious universities such as Harvard University, Boston University, and Taft University in the USA in addition to King Saud University in KSA. Dr Al-Roheimi never stopped serving his county and caring for his country men and women, he was the principal of the Saudi education center in USA; he cared for over 700 Saudi students in the USA. He is a good researcher, active member of seven Saudi associations to name few; national ethics committee, national committee for stem cell research, national H&R strategy, national clinical committee.

The Objective

The main objective of Saudi FDA as per Dr. AlRohaimi is to set the regulations and execute national food and drug strategies. The SFDA is the regulatory authority for products during its lifecycle. The SFDA regulations will include the four phases of product development; Premarketing, Standardization, Approvals and Post Marketing surveillance.

Dr. Al-Rohami realizes that education is the first step to develop a well informed and aware industry; researchers, investors and pharmaceutical professionals. Education and regulations is the magic components of a healthy professional medical society producing drugs, research and new products. So he emphasized the importance of training and continuous medical education; such as Good Clinical Practice, regulatory requirements, drugs lifecycle, pharmacovigilance, ets.

It is clear that Dr. AlRohami education and experience enabled him to master drugs life cycle process including clinical research in particular. So the SFDA will use the regulations in order to stop any illegal and unethical process during the lifecycle of a drug in KSA. The SFDA officials know that this is only the starting point of control, the system is flexible and focused to achieve the ultimate aim of preserving lives and maintaining good health of all individuals residing the Kingdom of Saudi Arabia.

Clinical Trials Registry

The new requirements with regards to notifying the SFDA of all clinical trials taking place in KSA had created many debates among the pharmaceutical industry; but it is proven that this is the first and most vital step to gain control current and ongoing clinical trials in the kingdom.

The SFDA have launched a new National registry for Clinical Trials in line with WHO recommendations to ensure that all clinical trials in KSA will be notified to the sFDA. Furthermore, Publications will not be accepted unless the clinical trial is registered.

National Pharmacovigilance Center request that all suspected unexpected serious adverse events and serious adverse events should be reported during 7 days and 15 days respectively. Safety and other electronic submission can be accomplished online using SFDA website electronic services. Adverse drug reaction should be updated in the Investigator Brochure at least once annually.

In Control

The SFDA official explained the role of 14 border laboratory in drugs and samples analysis, one of these labs is now active in KSA-Damam border. He also explained the regulations in regard to biological samples and when the conditions followed to evaluate the possibility of sending biological samples outside the KSA.

In regard to drugs, the SFDA is in the process of establishing a national drug codes for all medications marketed in the KSA, this enable tracking of drugs in case of potential recalls. Registration of medication will take place every 4 years; registered not marketed drugs for over 2 years will be queried by the SFDA resulting in the possible withdrawal of the registration status.

The discussion was informative in term of new regulations in the Saudi Arabia for New Investigational New Drug application, New Drug and Post Marketing research Application, Investigator initiated research. Fees structure of each type of studies, specific regulations for each type of studies, time frames of approvals and other regulations have been highlighted. ●

This interview was conducted by ClinArt International: Ms. Maha Al-Farhan, M.Phil, M.B.A, CCRA and Dr. Ranya Shahrouri, DVM, MBA/HCM, HDVP, Interviewed Dr AlROehimi alongside PABME conference that took place in Dubai-UAE May 2010.

This interview was conducted by: Ms. Maha Al-Farhan, M.Phil, M.B.A, CCRA and Dr. Ranya Shahrouri, DVM, MBA/HCM, HDVP, of ClinArt International with Dr. AlROehimi at the PABME conference that took place in Dubai-UAE May 2010.
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The Impact of Recent 'Biologicals' Legislation on Clinical Trials in Australia

PEER REVIEWED

The Australian government recently passed legislation concerning the regulation of human cell and tissue therapies. On 31 May 2010, the Therapeutic Goods Amendment (2009 Measures No. 3) Act 2010, which amends the Therapeutic Goods Act 1989, was signed into law. The new Act contains a number of amendments concerning the regulation of medicinal products, but its main focus is a new framework for the regulation of 'biologicals'. This article examines the potential impact of this biologicals framework on clinical trials of cell therapies in Australia.

The term 'biological' is generally considered to encompass most biological medicinal products, including traditional biotech products, such as recombinant proteins. However, the new 'biologicals' framework in Australia only applies to products containing human cells and tissues that are intended for a medical purpose, and does not affect the regulation of such biotech products. Furthermore, there are a number of exemptions for products that do contain human cells or tissues, as summarised in Table 1.

Now that the bill has passed, the Therapeutic Goods Administration (TGA) has one year to implement the framework, and there will be a three year transition period for existing products. This article is based on draft information that has been made available, which may be subject to change in the final implementation.

Regulation of Clinical Trials in Australia

In Australia, if a product is not entered on the Australian Register of Therapeutic Goods (ARTG) and is not the subject of the Special Access or Authorised Prescriber process, then clinical trials concerning that product must be regulated through one of two different procedures.

In the Clinical Trial Notification (CTN) procedure, the appropriate Human Research Ethics Committee (HREC) performs both the ethical and the scientific review of a proposed clinical trial, and the TGA is notified of the clinical trial if a positive decision is reached by the HREC. It should be noted that in some cases the TGA does request and review the trial documentation; in any case the TGA does have the power to halt a clinical trial. The CTN was originally intended for Phase III and IV and bioavailability/bioequivalence studies [2], but in practice it accounts for over 95% of Australian clinical trials and it is used for all phases of study, except for the most high-risk products, such as genetically modified organisms (GMOs).

The second procedure is the Clinical Trial Exemption (CTX), in which the TGA performs a scientific review of the trial documentation. While it differs significantly in procedural details, the CTX procedure is analogous to a Clinical Trial Application (CTA) in Europe or an Investigational New Drug (IND) application in the US, where the competent regulatory authority performs a technical and safety review. In general, the CTX procedure is more onerous for a sponsor of a clinical trial because there are more documentation requirements and the timelines are longer.

Scope of the Biologicals Framework

Four different classes of 'biologicals', or therapeutic goods containing human cells or tissues, are introduced by the framework, as summarised in. The biologicals framework does not affect the overall regulation of clinical trials in Australia but, depending on how the investigational product is classified, there may be some differences on the regulatory pathway that is taken.

Previously, tissues intended for transplantation that were not intentionally altered, such as dura mater, skin and corneas, were exempt from the requirement for entry on the ARTG, although they were required to comply with GMP. It is a requirement of the new framework that these types of tissues be entered onto the ARTG during the three-year transition period.

Some products containing cells or tissues of human origin were previously regulated as "therapeutic devices", and declared other therapeutic goods (OTGs) if the principal therapeutic purpose was not achieved through chemical, pharmacological, or metabolic actions. Under the framework, such products which exert their therapeutic effect through mechanical or other means will now be regulated as biologicals. This classification may help or hinder their use in clinical trials, depending on the extent of the manipulation of the cells/tissues.

Table 1 Scope of Biologicals Framework [1]

Included	Excluded
A thing that comprises, contains or is derived from human cells or human tissues and is used for a medical purpose*	Assisted reproductive technologies (self-regulated)
Some human stem-cells	Solid organs
Tissue-based products (bone, skin)	Fresh blood
Cell-based products	Xenotransplantation
	Single medical procedures
	Haematopoietic progenitor cells and blood

* Complete definition is found in section 32A of the amendment

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Table 2 Classes of biological products [1]	
Definition*	Requirements for inclusion on the ARTG
Class I (low risk)	
It is not banked It is not processed beyond minimal manipulation	Declaration of compliance with appropriate standards
Class II	
It is banked It is not processed beyond minimal manipulation	Demonstration of compliance with standards GMP conformance (TGA issued manufacturing licence) for cell banking facility
Class III	
It is processed beyond minimal manipulation but does not purposefully alter the biological activity	Demonstration of quality, safety and efficacy by submission of a dossier GMP conformance (TGA issued manufacturing licence) for manufacturing facility
Class IV	
It is processed in a manner that deliberately manipulates the biological property(ies); or The intended use is not its homologous function	Demonstration of quality, safety and efficacy by submission of a dossier including clinical data and analyses GMP conformance (TGA issued manufacturing licence) for manufacturing facility
* Products can be placed into a specific class by Order of the Secretary	

It should be noted that based on the draft guidance, there is no distinction between the classification of autologous and allogeneic products. Although the allogeneic therapies as a class of products are more likely to be significantly manipulated, they are not a priori classified as high-risk.

Low-Risk Products

For low-risk, class I and II products, the framework may facilitate the conduct of clinical trials, or even obviate the need to perform clinical trials in the first place. Provided that the product is manufactured in accordance with appropriate standards and a correct declaration or demonstration of compliance is supplied to the TGA, then the product would be entered on the ARTG and could be supplied commercially as an approved good. There would be no need to perform clinical trials to demonstrate the safety or efficacy of the product.

Should a sponsor wish to conduct a clinical trial then it would not be regulated by the TGA, provided the product is used for its homologous function. Such a trial would however require the approval of the appropriate HREC, and as such the regulatory burden on the trial sponsor would be equivalent to conducting the trial on any other new medicine through the CTN procedure.

Registration of a low-risk product requires that appropriate standards are in place. In late 2009 / early 2010, the TGA released draft standards for minimising infectious disease transmission, cardiovascular tissues, musculoskeletal tissues, ocular tissues and skin tissues. Along with existing standards for haematopoietic stem cells, these draft standards should cover most of the commonly used tissues. It is expected that other standards will be developed in collaboration with industry as they become required, but it should be noted that if a tissue does not have an applicable standard, then it may not be possible to register it as a biological on the ARTG.

Minimal Manipulation

From a sponsor's perspective there are advantages to classification as a class I or II product; the regulatory burden for conducting clinical trials is reduced, and it may not be necessary to conduct such studies at all. Therefore one of the key definitions in the new framework is that of "minimal manipulation", and the current proposed definition is provided in.

Table 3 Definition of "minimal manipulation" [3]
Minimal manipulation means a process involving any of the following actions:
Centrifugation
Refrigeration
Freezing
Trimming
Flushing
Washing
Simple milling
Any action similar to those mentioned above

At first glance the definition of minimal manipulation appears to be restrictive, but this does not necessarily prescribe that only simple products could be classified as class I or II.

Indeed, the EU advanced therapy medicinal product (ATMP) regulation (EC) No 1394/2007 has a similar list of minimal manipulations, and based on the European experience there is some scope for what appear to reasonably complex products. The following product was not classified as an advanced therapy medicinal product, i.e. the product was considered only minimally manipulated [4]:

"Product consisting of naturally occurring antigen-specific CD8+ donor lymphocytes isolated with Streptamers."

Thus it appears that reasonably complex purification procedures may be deemed minimal manipulation, allowing such products to be classified as low-risk. We recommend, however, that the sponsor consult with the TGA to confirm any such borderline classification.

High-Risk Products

If a product is manufactured in a manner that intentionally manipulates the biological properties, or if the intended use is not its homologous function, then the therapy would be classified as a higher-risk class III or IV product. These products will be regulated much like other medicinal products, and will require the demonstration of quality, safety and efficacy, submitted in a dossier to be reviewed by the TGA, before approval and entry onto the ARTG. Clinical trials using these types of products will still be regulated through the CTN and CTX procedures.

The framework appears to introduce two new considerations for conducting clinical trials with biologicals. The first is the possibility of conducting trials to demonstrate the safety of class III product, but not necessarily the efficacy, and the second is possible mandatory use of the CTX procedure for high-risk products. The proposed ARTG entry requirements for class III biologicals are the demonstration of quality, safety and efficacy, with the efficacy requirements based on clinical trials staged according to risk-based principles. For class IV biologicals, efficacy must be demonstrated by clinical data and analysis. Interpretation of these requirements at this draft stage is somewhat speculative, but it could be concluded that the efficacy requirements for class III biologicals could be fulfilled by a reduced clinical programme, and possibly literature from clinical trials using related products.

An example of such a product is cultured autologous chondrocytes for the repair of knee cartilage defects. The expansion of the cells in culture definitely constitutes significant manipulation, but the biological properties are not intentionally altered. There is also a significant body of literature supporting the safety and efficacy of these types of products. It would therefore appear reasonable that entry onto the ARTG could be supported by a relatively small, safety-focused clinical trial along with supporting literature. The authorisation in the EU of ChondroCelect, characterised viable autologous cartilage cells expanded ex vivo and expressing specific marker proteins, on the basis of a relatively small pivotal clinical trial, provides a precedent for this type of approval strategy [5]. If such a flexible approach is adopted by the TGA, then sponsors could be in the position to perform smaller safety-focused clinical trials to support registration of class III biologicals. The second consideration is that it appears likely the CTX procedure will become mandatory for clinical trials with high-risk biologicals. Although the exact scope of this requirement is currently unclear, such a rule would represent a significant increase in regulatory burden for sponsors who might previously have been eligible to use the CTN procedure.

Overall, the decision of whether to use the CTN or CTX procedure has depended on the sponsor and the HREC that reviews the clinical trial documentation. For more complex or advanced products, the CTN procedure may still be suitable if the HREC has access to the appropriate scientific and technical expertise in order to assess the safety of the product. A CTN application can be deferred to the CTX procedure at the discretion of the HREC. Although the actual regulatory procedures used for specific clinical trials are not published, per se, it is understood through verbal communications, for example at conferences, that a number of clinical trials involving manipulated and expanded cells have been initiated based on the CTN procedure. It is possible that such products will be considered high-risk in the future, and may be subject to the CTX pathway once the biologicals framework is implemented.

If, however, the scope of the mandatory CTX procedure is restricted to genetically modified or otherwise highly manipulated products, then it will have little practical impact, because few such products are at the clinical stage in Australia, and they would have likely used the CTX procedure anyway.

Summary

Legislation concerning the regulation of medicinal products containing human cells and/or tissues was recently passed by the Australian government. A new classification system will be introduced but, for the most part, the biologicals framework serves to clarify, update and consolidate previous regulations rather than implement a new regulatory regime. The regulation of clinical trials in Australia through the CTN and CTX procedures will remain unchanged. The framework now provides a pathway for the entry of minimally manipulated cells and tissues onto the ARTG. Some borderline products may benefit from the clarified definitions and be classified as low-risk, class I products. Clinical trials using such products would generally be regulated at the level of the local ethics committee. The possible impact on higher-risk cellular therapies is of considerable interest, but at this stage not completely clear. There is the potential for relatively small, safety-focused trials to support the registration products, where the cells are manipulated but their biological function is not altered.

It is also proposed that it may be mandatory for some cell-based therapies to be studied under the CTX procedure where, currently, the CTN procedure can be applied. In Australia, most sponsors of these types of products are academic institutions and, depending on the scope of this requirement, the regulatory burden to conduct a clinical trial could dramatically increase. ●

References:

1. Adapted from Smith G (2010) Regulation of cell therapies, presented at The Fourth Margaret River Forum - Pathways toward Molecular and Cellular Therapy, International Society for Cellular Therapy, Margaret River, WA, 30 April 2010

2. Access to Unapproved Therapeutic Goods - Clinical Trials in Australia (2004)

3. http://www.tga.gov.au/bt/hct.htm - accessed 29 June 2010

4.http://www.ema.europa.eu/htms/human/advanced_therapies/recommendations.htm - accessed 29 June 2010

5. European EPAR for ChondroCelect

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Dianne Jackson-Matthews, currently is Director of the ERA Australian office, and was Director of the Washington DC office from 2001 to 2004. Dianne has worked closely with companies in the Asia-Pacific region, to ensure their biological products have been developed in line with the European and US requirements. Prior to joining ERA, Dianne spent 20 years in the US, including senior positions in the biotech industry. Most recently she was the Director of Global Regulatory Affairs at Unigene Laboratories, Inc., New Jersey, USA, where she also gained extensive development experience in GMP production and testing of biotechnology products.
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The Need to Educate and Empower Clinical Research Professionals in Emerging Markets

The strength of the clinical research industry in emerging markets such as Latin America, the Middle East, Africa, India and China rests on the solid foundation of quality education and training in all aspects of clinical research. Being well informed empowers all involved in clinical research to actively participate and contribute to the whole process of drug development. The number of local trained investigators and clinical research professionals is an indication of the level of development of that region.

The imparting of knowledge in clinical research to regions that are naïve in conducting studies is important, as it plays a very decisive role in the growth and development of the field in these regions. The ICH/GCP and international guidelines mandate that only well qualified and trained personnel should conduct clinical trials. It is therefore very important to ensure that training and development of the emerging markets is being considered on a priority basis. Training is also mandatory in order to maintain quality and consistency in global clinical trials. As such there are several training modules currently being offered by global contract research organisations (CROs) that conduct quality training.

Identifying the Need for Training in Emerging Markets

Pharmaceutical companies have realised the needs and benefits of investing in clinical research in the emerging markets and as such, many studies are being planned for the near future in these regions. The emerging markets have recently become more in demand, and therefore training needs must be carefully addressed in these developing regions.

A mismatch between the number of trials planned for a region, and clinical research professionals available to carry out these studies, can have serious implications on the progress and success of the study. This necessitates training and development of the region. Many pharmaceutical companies and global CROs with an established presence in the emerging markets have taken on this initiative to ensure that relevant personnel are well trained, thereby making their country more attractive for actually investing in clinical research.

By ensuring that training and development are implemented into the study plan, and by imparting knowledge to the developing regions, a relationship is then forged between the investigators, study site personnel and the trainers. In order to address the importance of this, most global CROs have now added a 'Learning and Development' department as one of their service arms.

Analysis of feedback from a recent training session - 'Regulations, Monitoring and Quality in Clinical Research' - in Dubai, UAE, showed that the candidates have expressed a need for more frequent and in-depth clinical training. This would not only give the participants of such training a chance to better understand the requirements of performing good clinical research, but would also refresh those who have been in the field for a longer period of time. Countries within the emerging markets are placed at the forefront of the expanding clinical research field, and therefore require well trained personnel to handle a higher influx of trials and to provide credible data on the safety and efficacy of drugs.

Identifying Potential Ways to Train and Develop Emerging Markets

It is important for sponsors of clinical trials to identify potential ways to develop the regions they plan to invest in. A few ways in which market leaders could develop emerging markets include:

- Collaborating with the regulatory authorities of the developing markets to impart training on international regulations and guidelines
- Training of institutional review boards (IRB) and ethics committees (ECs) to ensure that their constitution and functioning is in accordance with the ICH/GCP guidelines
- Training of candidates in order to make up for skills shortages, and provide career development to retain them.

Global CROs with an established presence in the emerging markets have dedicated highly-qualified trainers with vast global experience in educating the clinical research professionals of

the emerging markets. Using the services of these trainers can accelerate knowledge growth and increase the quality of clinical research in the emerging markets.

In order to address the individual needs of the range of professionals conducting clinical studies, areas of training can be separated as follows:

- Regulatory authorities

A few of the developing regions have realised the need for a regulatory authority to keep a close view on clinical trials conducted in the region. As a result, much time and effort is being spent currently on training the professionals to have a deep understanding of the processes involved in clinical trials, and the review process that they would be involved in. Adequate training is important to take these newly-established regulatory bodies to meet the competency of high-level global research and match the international standards of the established markets.

- IRBs/ECs functioning as per ICH/GCP guidelines

Courses covering advanced issues in research ethics to address ECs in the emerging markets aim to freshen experienced committee members and provide guidance to anyone with a serious interest in the work of research ethics committees. Training to address in this area includes: informed consent, ethical issues in particular areas of research, the role of assent in child research, retained tissues, genetic research and xenotransplantation can all provide useful sessions to build up the knowledge of ECs.

- Principal investigators & co-investigator training

Intensive courses for clinicians assuming principal investigator responsibilities for clinical trials are required in developing regions to ensure their competency. As PIs, they are also required to possess the valuable skills and knowledge of prevailing international and regional regulations in order to conduct well-organised and controlled clinical research studies within their institutions.

- Study site personnel

Training of site personnel and preparation of the site to take on global trials are top priorities. As these sites are very new to the whole concept of clinical research, it is very important to have a team of trainers give them the most suitable kind of training; whether this be classroom-based, online or training by the monitor. Once the sites are confident enough and well experienced in conducting global trials, web conferences or investigator meetings can be used to strengthen these foundations. At the initial start-up phase however, the presence of trainers and availability of training material is important. This training should encourage interactive participation and keep the site personnel engaged during the process.

- Project Managers, CRAs, CTAs

Training in the fundamentals of clinical research, including history of legislation and regulations that govern clinical research and an overview of drug, biologic, and device development, is vital for those responsible for monitoring and running the study. Imparting thorough knowledge of Good Clinical Practices and International Conference of Harmonization guidelines (E6, E2A) allows participants to gain a solid understanding of clinical trial development and advanced courses for project managers in the management of clinical trials.

There is an urgent need for a local presence of global CROs with trained and qualified project managers, clinical research associates and trial assistants within the emerging markets.

What can be done to Increase an Emerging Region's Ability to Learn?

There are two fundamental issues in clinical research training; knowing the work practices of the region, and creating a learning culture. It is therefore important that trainers have a thorough knowledge of the local regulations in addition to the international guidelines. Global CROs and pharmaceutical companies in the emerging markets have had the ability to sense and respond to the needs of these markets with ingenuity and speed, allowing training sessions to be adapted to include regional regulations and tailor-make sessions for each country.

Culture in the Emerging Regions

It is important to take cultural differences into consideration, as in different regions people learn and communicate in various ways. Local country managers for each region can best provide the input on the culture of the participants, and this valuable information can be considered while tailor-making courses for different areas. It is also advisable to conduct a survey by giving out participant feedback forms once the training courses have ended, to identify potential areas of improvement for each training session.

Language

Though English is the medium for training in the emerging markets, it is important for trainers to speak slowly and clearly, as many participants may not be fluent. To be able to adapt quickly and in regions that undergo rapid change of regulations has been challenging, but nevertheless rewarding.

If those involved in conducting clinical trials are able to train and impart their knowledge to the regions in need, this then forms a backbone of the survival and growth strategy for the clinical research industry. Identifying the needs of the emerging markets and tailor-making training sessions based on these needs, taking into consideration the local culture and regulations, is challenging, but end results are rewarding. Therefore by having established a Global Academy for Clinical Research Excellence (ACRE) that trains in different aspects of clinical research in the emerging markets, ClinTec International has been able to witness the implementation of its vision.

Rani Abraham M. Pharm - Associate Director - Regulatory Affairs and Operations Rani Abraham is ClinTec's Regional Manager for the MENA region bringing with her over 13 years experience in the clinical research field. Rani has strong experience in both Regulatory and Ethics submissions in the Middle East, with experience in writing SOPs for both the Institutional Ethics Committees and CRO's. She has worked on multiple multinational trials across a variety of indications and therapeutic areas including Cardiology, Psychiatry, and Endocrinology. Prior to joining to ClinTec, Rani worked as a CRA for Global pharmaceutical companies and as a Medical Research Co-ordinator for the Dubai Health Authority as a member of the Medical Research Ethics Committee and holds a certificate in GCP from the Thrombosis Research Institute, London.

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Clinical Trials in China

China – What's all the Fuss About?

Not only does China have great market potential and is fast becoming a manufacturing powerhouse for the global pharma industry, but it is also being recognised as the future epicentre of research & development. The drug discovering capabilities of China are considerably more desirable when considering its already obvious advantages in cost. Conducting R&D in China can save research costs by up to 60 %, and drug developers can expect typical savings of 30 % compared to Western costs.

In 2008 it was predicted that China would be the world's third largest prescription drug market by 2011. A report released by IMS Health (a pharmaceutical market research firm) shows that China's pharmaceutical revenue is growing fast, and the market may double by 2013. The domestic pharmaceutical industry has been a key contributor to the country's impressive economic growth, which has made China the world's fastest growing pharmaceutical market.

Clinical Trials in Asia

With the costs of technology rising steadily, and regulatory requirements tightening throughout the EU and US, drug development in these regions is starting to dwindle. It is becoming increasingly more time-consuming and costly to initiate a clinical trial, particularly now that pharmaceutical companies are faced with price pressures from the healthcare markets – forcing them to tighten their margins and therefore limiting growth opportunities. For this reason, China is becoming increasingly attractive to big companies looking to reduce these constraints. The global balance is shifting in China's favour and with this, scores of Western-trained scientists with pharmaceutical expertise are choosing China as their study destination.

So as you can see, Asia is fast becoming an international hub for clinical trials. China, India, Korea and South East Asia are all key regions for development. Most big pharmaceutical companies have now expanded into Asia, taking advantage of the cheaper labour costs and rapidly expanding market intelligence. However, these benefits can come hand in hand with some complications; the regulations for importing and exporting out of Asia, particularly China, are considerably more complex than elsewhere.

The Difficulties with setting up Clinical Trials in Asia

Presently there is a significantly longer process involved for granting import/export approval for drugs in China than there is elsewhere in the world. Even within Asia, China has by far the longest processes. The biotech industry is still very new to China and the Chinese Government. Although progressing at a rapid pace, processes are still being designed and optimised. Some applications still require 'hand by hand' operation and cannot be completed online.

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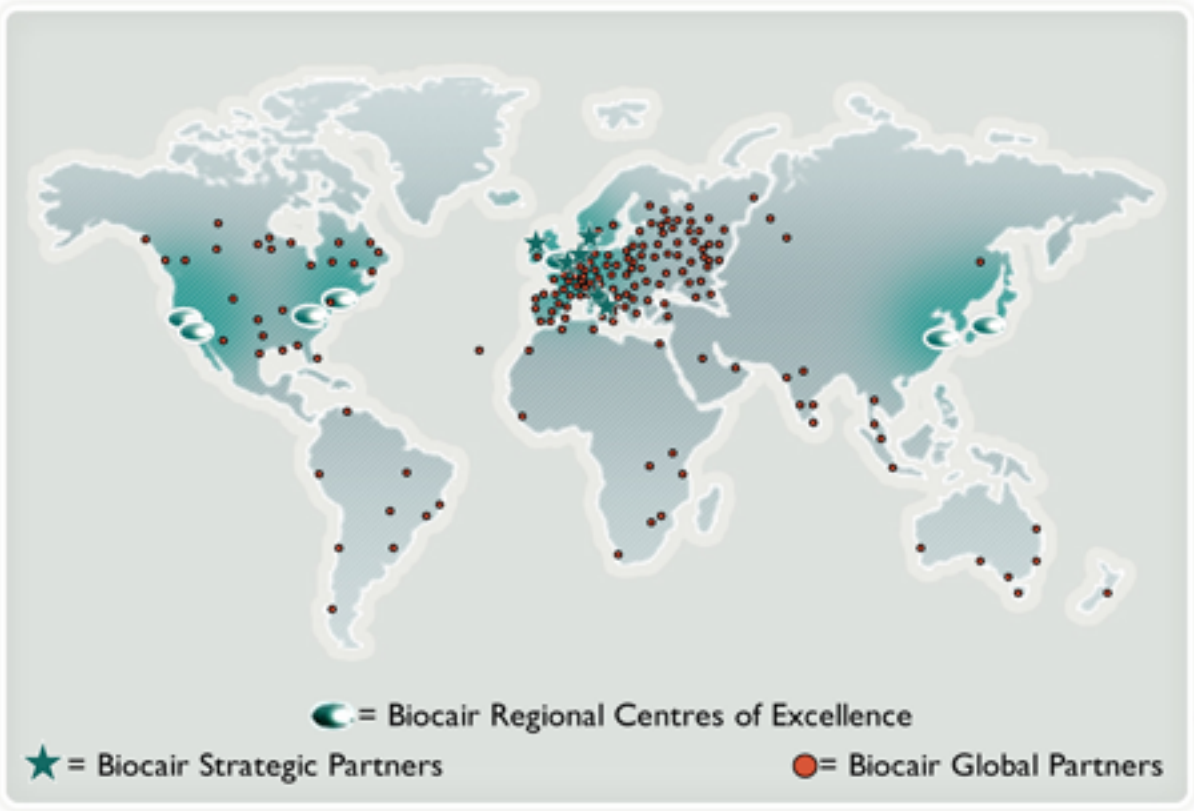

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The average time it takes to gain regulatory approval for a clinical trial in China is nine months. India is roughly two years ahead of China, and has made marked improvements to its processes in this time. Obtaining approval here now only takes two to two-and-a-half months. But for clinical trials, the process is prolonged further as approval must be obtained from the DGFT (Directorate General of Foreign Trade), which can take between one and two months. With the steady increase in clinical trials applications in Asia, the DCGI (Drugs Controller General of India) has become more experienced and ploughed more money into resources, thus rapidly reducing approval time.

Korea (closely followed by Singapore) is the most developed country in Asia in terms of pharmaceuticals and regulatory processes. Here the average time for granting regulatory approval for a clinical trial is just 30 working days. In Singapore, it takes roughly a month for regulatory approval, but it takes a further month to obtain approval from the EC (Ethics Committee). On the other hand, in Hong Kong these processes can run at the same time, thus reducing approval time for both to an average of nine weeks. Then a licence to import a clinical trial must be granted, which usually takes two weeks.

The above goes some way to illustrate how difficult it is to set up a clinical trial in China. However, clinical trial logistics can be tricky wherever they take place. Below is a simplified example of the steps that a specialist logistics courier would take when organising a clinical trial movement from various European destinations and delivering them to a research laboratory in China:

Moving a Clinical Trial to and around Asia

We will start at the beginning: Pharma Co. are conducting a clinical trial in clinics across Germany, Switzerland, Belgium and Poland. They need to move the various samples collected to their research laboratories in Shanghai, China.

- Pharma Co. would go to a specialist courier like 'ABC123 Courier' and request a quote.
- Pharma Co. can quote for an individual shipment within the trial, or can quote for the movement of the entire clinical trial.
- This will include multiple collection points and consignees across the globe.

In this instance, Pharma Co. would like ABC123 Courier to organise the movement of the entire trial.

- For ABC123 Courier to provide a quote, they need to be able to classify the product(s) being shipped.
- If Pharma Co. provides a detailed description, then the courier can classify the product more quickly.
- If a description is not provided then ABC123 Courier must research the product on behalf of Pharma Co. in order to classify it correctly.
  -The time involved in this process is dependent on the complexity of the product.
- Once the product is classified, ABC123 Courier will suggest and provide appropriate packaging so that the product arrives at Pharma Co.'s Research Laboratory in Shanghai in perfect condition.
  - For example, some products need to be shipped in a temperature-controlled environment.
- ABC123 Courier must now design a route for the shipments that ensures they meet their required delivery schedule, as outlined by Pharma Co.
- ABC123 Courier must now go back to Pharma Co. with the proposed routing, packaging and classification to receive authorisation on the shipments.
- Pharma Co. can track the shipments with ABC123 Courier's Track & Trace facility on their website.
- Once the shipments have arrived at Shanghai Airport, it will go through Customs and providing the product(s) has been classified accurately and all permits are in place, there will be no delays.
- ABC123 Courier's Chinese transport unit will pick the shipments up and take them to their final destination.
- ABC123 Courier and Pharma Co. will both receive confirmation that the shipments have arrived.

This process seems simple enough when broken down as above, but various timelines have not yet been considered. Regulatory approval has to be obtained and we've already discussed how this can be a lengthy process. As explained above, gaining regulatory approval for importing samples to Asia is a longer process than most continents, but China can be particularly difficult. This can be for many reasons, including:

- The fact that the industry is still relatively new to China.
- Their stringent import and export rules.
- The amount of regulatory bodies to gain approval from.

With so many bodies to gain approval from, there are far more opportunities for delays to occur – and this is something that pharma companies need to be aware of and factor in when involving China in a clinical trial. For example, when choosing a specialist courier, it is wise to consider more than the price. A good specialist courier will have an in-depth knowledge and thorough understanding of all local regulatory bodies and their requirements, thus ensuring the process is as swift and efficient as possible.

As mentioned above, this process takes varying amounts of time in different countries in Asia. For example, both Korea and Singapore have relatively quick regulatory processes, and are able to deliver clinical trial approval within 30 working days.

In Conclusion

In 2008 we were predicting China's success for 2010/11 – getting ready to jump on the back of the wave. Well, now we're here and we need to start recognising that China IS the international hot spot for pharmaceuticals. Get your surfboard out and get involved.

Harriet King, Marketing Executive. Biocair International. Recently graduated with a degree in Marketing, Advertising and PR; Harriet brings a fresh look to Pharmaceutical Marketing by combining traditional marketing techniques with New Media practices. During her education, she worked with a number of PR & Events agencies and spent a year with car giants BMW MINI, before making her debut in Pharmaceutical Marketing with Biocair.
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Clinical Trials in Africa: Some Translation Issues

The days when medical research was primarily done in the USA or in Western Europe are ancient history. For a number of reasons, both medical and financial, more and more clinical trials are conducted in other countries, turning the trials into international projects. International trials are almost by definition multilingual trials, which is why experienced medical translators have to be involved.

In medical research a number of different documents play an important role. The principal document which is used to inform the authorities about the trial, and to convince them to allow it, is the *Study Protocol*, describing the background and purpose of the clinical trial, the anticipated outcomes, the profile and recruitment of patients, insurance issues etcetera. In many countries in Africa, CROs can provide the text of this document in English or in French. For study participants, the most important document is the *Informed Consent Form* (ICF), which is used to inform a target group, usually patients suffering from a certain disease or condition, about the study and to invite them to participate. Under the Declaration of Helsinki, developed by the World Medical Association in 1964 (and frequently updated since then), participants must be fully informed and must completely understand the information, including the risks associated with the study medication or study treatment. In most cases this means that the ICF has to be available in their own language or dialect. This turns a trial in Africa into something like a linguistic challenge. Participants must sign this form to state that they understand the information that was provided and that they are willing to participate. Other documents for patients/participants are *Patient-Reported Outcome* forms (PROs), such as *questionnaires* or *scales*;

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Africa: Continent of Linguistic Variety

Let's take a look at Africa from a translator's point of view. As far as population is concerned, Africa numbers over 50 different countries, and has a total population of almost one billion (twice the size of the European Union). The top three countries account for one-quarter of the total population of Africa: Nigeria (130 million), Egypt (72 million), and Ethiopia (70 million).

One-third of the 6000 or so different languages worldwide are spoken in Africa. On top of these 2000 languages, there are tribes that communicate using a variety of different sign languages; some tribes use languages that are whistled (in order to communicate over longer distances!). Obviously, not all 2000 languages are equally important for commercial purposes, and the sign and whistle languages also do not play a role in medical research.

Most African languages belong to one of the four major language families:

- the Niger-Congo language family, with 400 million speakers in the Southern half of Africa
- the Afro-Asiatic language family (with 375 different languages) spoken by approximately 300 million persons in the Northern half of Africa
- the Nilo-Saharan languages, over 100 different languages spoken in Central and East Africa
- the Khoisan language family, spoken by 30 million people in Namibia and Botswana.

It is generally agreed that there are 85 'important' languages, which together cover the majority of the population of the continent. When taking only the official languages of the African countries into account, the total number of languages is restricted to less than 30, including the 11 official languages of the Republic of South Africa. In several countries, English, French, Portuguese, Spanish or Arabic is one of the official languages. The working languages of the African Union (AU), with 53 member states, are Arabic, Swahili, English, Spanish, French and Portuguese. It may seem strange that in this day and age, five of the six working languages of the African Union are non-African, but the advantage is that these languages are what one could call a common denominator. Of the AU working languages, Swahili is the only original African language: it is spoken by 5 to 10 million people as their first language, and by 80 million as their second language.

these are either filled in by the participant or, on the basis of an interview with the participant, by the investigator.

Writing such documents is one thing; translating them into all languages concerned is another, especially when African languages are concerned. Guidelines with strict translation requirements have to be followed, and study organisers need to obey these rules, or else they run the risk of having their study proposal rejected or – even worse – not having their study results accepted.

Translation Guidelines – The ISPOR Way

The *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR) has done a great job evaluating a dozen existing guidelines concerning the translation of patient-reported outcomes (PROs), and formulating an integrated method to produce language versions of PROs. The guidelines are based upon the rather strict translation requirements defined by organisations such as EuroQoL (European Quality of Life, the developers of the widely used EQ-5D questionnaire), EORTC (European Organisation for Research and Treatment of Cancer, the developers of several Quality of Life questionnaires), and IQOLA (International Quality of Life Assessment, the developers of the widely used SF-36 Health Survey).

The method recommended by ISPOR starts with a double translation, which is when two independent translators each produce a translation into a target language. To distinguish these translations from the back-translations that are made during the process, they are referred to as 'forward translations'. Next is a reconciliation of the two translations into one version, a double back-translation of the reconciled version, a reconciliation of the two back-translations, a final review, and a harmonisation across all language versions. While this can be considered the 'optimum' way to perform linguistic validation, it is a time- and cost-intensive process. The translation effort for a questionnaire that follows the ISPOR procedure is at least five times as high (and costly) as for a single forward translation and edit. Some argue that this additional 400 percent can be used in different ways to reach the required level of quality. If the ISPOR method is chosen only to find errors in the forward translation, this indeed is overkill. However, if it is used to make sure that a translated questionnaire is fully equivalent to the original, it does make a lot of sense and the ISPOR way is best.

Back-Translations

Back-translations are almost uniquely used in medical research; fellow translation providers tell me that this method is hardly ever used in translations for other industry sectors. For those who are not familiar with the concept: a back-translation is a translation of a translated text back into the language of the original text, made without reference to the original text. The idea is that the author (or trial sponsor) can verify whether the translation covers all aspects of the original. As such, back-translations are part of the process of generating translated versions of a document; the purpose is not just to check the quality of the original translation. If back-translations are merely done to keep on file in case of an FDA inspection, or to satisfy ISO auditors, the extra effort and cost are a total waste. Only when taken seriously and done in a professional way is a back-translation effective, able to identify shortcomings of a translation and, more importantly, able to produce a quality instrument.

Back-translations from African languages have an extra layer of complexity, namely that the guidelines require the involvement of native speakers of English, who have studied an African language long enough to qualify as a translator and who understand the topic well enough to be involved in a back-translation. In a country such as South Africa, very many people speak excellent English and a back-translation from, for example, isiZulu into English would not be a problem. Yet this is different for many other African languages, as there are very few native speakers of English who have studied an African language. And understandably so: there is hardly any demand for translations in this language combination, so even if translators do exist, they are probably not very experienced. (Actually, this same problem also exists for back-translations from EU languages such as Lithuanian or Maltese.)

Forward translations are much less of a problem. There are plenty of professionally trained and experienced translators in many African countries who can translate from English (or some other language) into their native language. Their main drawback is limited access to fast internet.

Home Language	Black	Coloured	Indian or Asian	White	Total
Afrikaans	0.7 %	79.5 %	1.7 %	59.1 %	13.3 %
English	0.5 %	18.9 %	93.8 %	39.3 %	8.2 %
IsiNdebele	2.0 %	0.0 %	0.3 %	0.1 %	1.6 %
IsiXhosa	22.3 %	0.3 %	0.1 %	0.1 %	17.6 %
IsiZulu	30.1 %	0.3 %	0.2 %	0.1 %	23.8 %
Sepedi	11.9 %	0.1 %	0.0 %	0.0 %	9.4 %
Sesotho	10.0 %	0.2 %	0.0 %	0.0 %	7.9 %
Setswana	10.3 %	0.4 %	0.0 %	0.1 %	8.2 %
SiSwati	3.4 %	0.1 %	0.0 %	0.0 %	2.7 %
Tshivenda	2.9 %	0.0 %	0.0 %	0.0 %	2.3 %
Xitsonga	5.6 %	0.0 %	0.0 %	0.0 %	4.4 %
Other	0.3 %	0.2 %	3.8 %	1.1 %	0.5 %
Total	100 %	100 %	100 %	100 %	100 %
	35.42m	3.99m	1.16m	4.29m	44.82m

Translation of PROs

Patient-reported outcome (PRO) forms, such as questionnaires, are the most important documents in clinical trials. They are used to collect information from patients, either directly (by patients filling in the questionnaire) or through an investigator or interviewer who records the patient's responses onto the form. PROs are most often used to collect information on quality of life (QoL) in general, health-related quality of life (HR QoL), disability, and physical or mental symptoms of disorders or conditions (for example asthma, migraine, urinary incontinence). The information collected using PROs is fed into a database, which is then used for further research.

The original version of a PRO is usually the result of a joint effort by several researchers who spend a lot of time and energy in generating a high-quality instrument. The authors pay a lot of attention to the precise wording of the questions and – in case of multiple-choice – the answers. It is then heavily tested, both on understandability of the questions and on measurability of the outcomes.

Producing a PRO is one thing: it is a complex matter requiring a lot of skills from different disciplines. Producing multiple language versions of a PRO is an even more complex matter: this is considered to be one of the most sensitive challenges for translators. It is never just translation; it is always translation plus adaptation to a specific region, or *locale* (this process is also referred to as 'localisation'). During localisation, many different issues need to be taken into account, and while language is important, it is certainly not the only issue. Other issues concern culture, literacy levels, understanding of certain concepts, and so on.

The overall quality (including both the linguistic aspects and the regional adaptation) is crucial for PROs. Questionnaires have to reflect all the fine nuances of the original. If questions in the questionnaires are not translated the exact same way across all languages, there is the risk that the answers to these questions cannot be pooled, and that parts of the valuable research data become useless. On the other hand, the wording of certain questions may be culturally sensitive or unacceptable in specific regions, and therefore these questions need to be revised.

Translation quality is also important because human patients and volunteers, who have the right to be properly informed, are involved. Also, trial results are often scrutinised by the authorities, and if they find something that is not in compliance with the rules, part of the research data may not be usable.

Cognitive Debriefing

After the translation/back-translation process is completed, the final version of the translated questionnaire is often tested. In the world of clinical trials this is usually referred to as 'cognitive debriefing'. During this phase, participants are interviewed on the basis of the translated questionnaire to check whether the questions can trigger the correct answers and, in case of multiple choice answers, whether or not these are clear enough. The participants are monitored for any sign of stress or discomfort, and the interviewer asks questions about the meaning of certain words used in the questionnaire to make sure that the questions are fully understood and not offensive in any way. The bottom line is that all questions in all language versions used in the clinical trial have the same meaning; this is called 'linguistic equivalence'. If not, the answers in Zimbabwe cannot be combined with those in Egypt, Morocco, or Namibia. For a trial that may include thousands of participants across a range of African countries, one cannot dedicate enough effort to this test phase!

Cultural Issues

When translating questionnaires into African languages, finding the right words may be a problem. English is much richer than many other languages, and some English words may not have a translation equivalent. On top of that, there is context and

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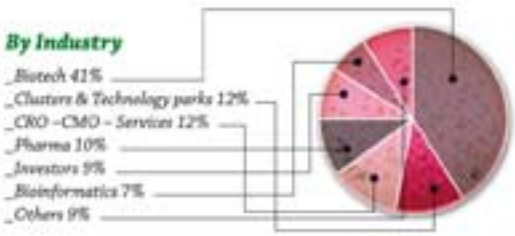

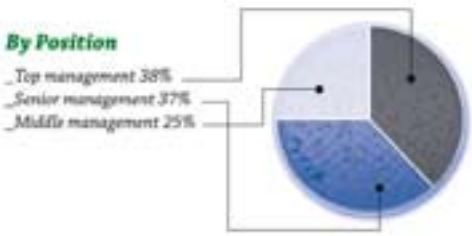

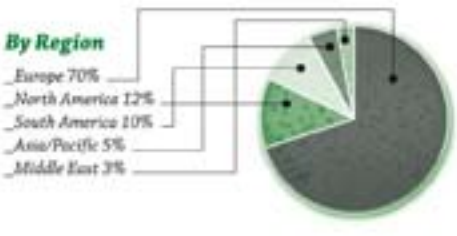

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cultural sensitivity. For example: a question about how a patient felt during the previous week had several multiple-choice answers. One of these was 'I was confined to bed'. It is not too hard to translate this phrase. However, during the process it appeared that there are two problems. First of all, not everybody in Africa sleeps in a bed. Secondly, in some cultures, being confined to bed means that one is about to die. The translation of this possible answer was then revised to something like 'I could not even walk'. Also, simple words such as 'a little' or 'quite a bit' as elements of multiple-choice answers sometimes prove difficult to translate, as do health states such as fatigue or levels of pain.

Questions such as 'Did you feel uncertain about your future' and 'Did your outlook on the future worsen?' also caused problems. These questions have a different impact in different countries. There are probably more people in Zimbabwe than in France or Germany whose future is not so bright in the first place. And what is seen as an acceptable setback for an average person living in a township in South Africa may be perceived as a catastrophe by a person living in Paris or Berlin …

Not Discouraged by Linguistic Challenges

Despite the linguistic challenges, the reasons why CROs organise trials in Africa are clear: first of all, there are certain diseases in Africa for which a cure has yet to be found. Also, there are of course plenty of people out there who do not incur high costs that need to be reimbursed, governments in many countries are cooperative, and there is a variety of diseases the Western world is no longer familiar with. In short, Africa offers almost ideal circumstances for clinical studies that require large study populations.

There are a few disadvantages, though. One is medical: malnutrition and co-morbidity make some of the trial participants less ideal. Another one is communication (limited access to fast internet) and infrastructure: it may be too much of an effort for participants to reach a study centre if they live half a day's ride away. And then, of course, there is language. Even within one country, most people will normally speak just one of many different languages or dialects. The official language is often a *lingua franca*: it is taught in schools and people can speak and understand it, but in most cases it is the second language and therefore it can hardly be considered as 'native language'.

Around 2000 different languages are spoken in Africa. Of these, some 85 are considered important languages. When counting the official languages only, this number is reduced to around 30, and the African Union only has six working languages (see separate text box).

Reducing the number of languages from 2000 to 85, 30, or even six does not help trial organisers who need to facilitate one-on-one contacts with participants who have to be addressed in their own language. And that is where the problem starts. In Nigeria, for example, there are over 250 different languages (which makes it a country with one of the greatest concentrations of linguistic diversity in the world). Organisers of trials in Nigeria would prefer to include only those participants who speak one of a limited number of Nigerian languages, thereby excluding many other populations.

Another example is South Africa, with 11 official languages (while we in Europe think that Belgium is already complex with three languages, or Switzerland with four …). Clinical trials in South Africa mainly use English, Afrikaans, isiXhosa and Setswana; the vast majority of the population speaks at least one of these languages.

The 'translation infrastructure' in South Africa as well as in several (but not all) other countries in Africa is rather well-developed, with many university-trained translators, and recruting quality translators should not be too hard. A problem is that in many regions in Africa, access to fast internet is not widely available.

Translations for clinical trials are usually not the typical 'few cents per word' type of translation projects that many translation agencies would be eager to accept and promise to turn around in a few days. It is best to stay away from providers who do not show any hesitation at all and who do not seem to realise that producing an African language version of a PRO (or any other clinical trial document) is in fact a big challenge – one that can only be completed successfully when done with the utmost care. ●

I thank Mrs Sandra Nortje, our translator in South Africa, for her contributions to this article.

References:

1. African languages. Information on African languages can be found at Wikipedia http://en.wikipedia.org/wiki/African_languages

2. Jelsma J, et al, 'A bridge between cultures: a report on the process of translating the ED-5D instrument into Shona'. South African Journal of Physiotherapy, 2000, 56, 3-9.

3. Wild D, et al, 'Principle of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation', Value in Health, 2005, volume 8, issue 2, pp. 94-104.

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Patient Recruitment Trends

The Impact of Clinical Trial Globalisation on the Enrolment Process

PEER REVIEWED

The greatest challenge facing clinical trial patient recruitment today is the globalisation of the clinical research enterprise. In the 10-year period between 1995 and 2005, the number of countries serving as trial sites outside the United States more than doubled.1 By the end of 2010, the top pharmaceutical companies are expected to conduct 65 percent of their clinical trials abroad.2 Sponsors of clinical research have been expanding into emerging markets, in part with the hope that accessing new patient populations will provide the silver bullet for on-time trial enrolment. But in fact, the percentage of studies that complete enrolment on time is extremely low in all of the world's clinical trial markets: 18 percent in Europe; 17 percent in Asia-Pacific; 15 percent in Latin America; and 7 percent in the United States.3

The root problem causing such overall poor study completion rates across the globe appears to be operational complexity. As sponsors of clinical research increase the number of countries in which they simultaneously conduct one study or a suite of studies, the layers of complexity expand exponentially for all study processes, including recruitment. The study leader is faced with orchestrating not only the horizontal functions of the study across countries, but the vertical detail of all functions within each country. And because recruitment spans a range of these functions – from planning and feasibility to site selection and outreach to patients – recruitment efforts are even more difficult to plan for and manage efficiently. Factors that guide the recruitment of a multinational trial include:

- Regulatory hurdles – per-country approval of the protocol and patient-facing recruitment materials
- Other start-up issues – site contracting, drug import/export, site staff recruitment training
- Recruitment environment – healthcare system variations among countries, availability of drug supply, standards of care, physician and patient attitudes
- Investigator selection – availability of qualified investigators and their suitability for a particular protocol
- Recruitment strategies – tactics and tools that acknowledge the motivations of patients and referring physicians (which may or may not align with the sponsor's scientific goals)
- Patient communications – cultural influences on communication between investigators and patients, as well as the acceptability of direct-to-patient outreach (including advertising)

To better understand these study leader concerns as they relate specifically to recruiting patients into global trials, BBK Worldwide conducted a survey of clinical research sponsor and clinical research organisation (CRO) representatives from around the world. What follows is a discussion of the survey results and their implications for the discipline of patient recruitment with the goal of improving on-time and on-budget clinical trial enrolment. BBK Worldwide's objective in conducting and sharing this research and resulting recommendations is to contribute to the dissemination of ideas for standardising recruitment for the clinical trial industry as a whole.

Survey Methodology

In 2009, BBK Worldwide surveyed 115 representatives from the clinical research industry. Eighty-four percent of respondents were clinical sponsor representatives, and 16 percent worked for CROs or site management organisations (SMOs). Topics focused on gaps in global patient recruitment, including strategic development and implementation, recruitment data management, and recruitment tactics. Survey questions were multiple choice, with the option to choose more than one answer. Hence, percentages do not add up to 100.

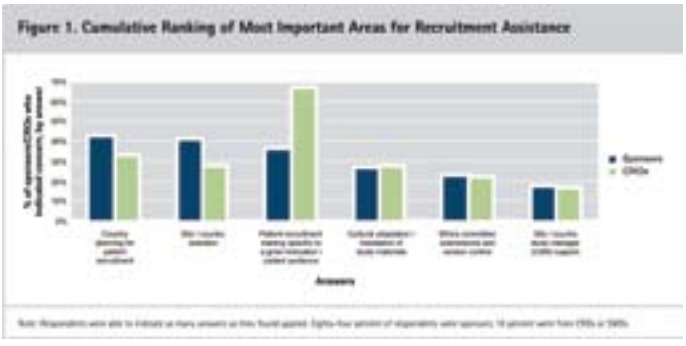
Results and Analysis

Responses from sponsors and CROs to all questions followed the same general patterns for ranking important issues. There were some significant differences, however, between the two audiences that reflect the variance in the purpose of each type of entity.

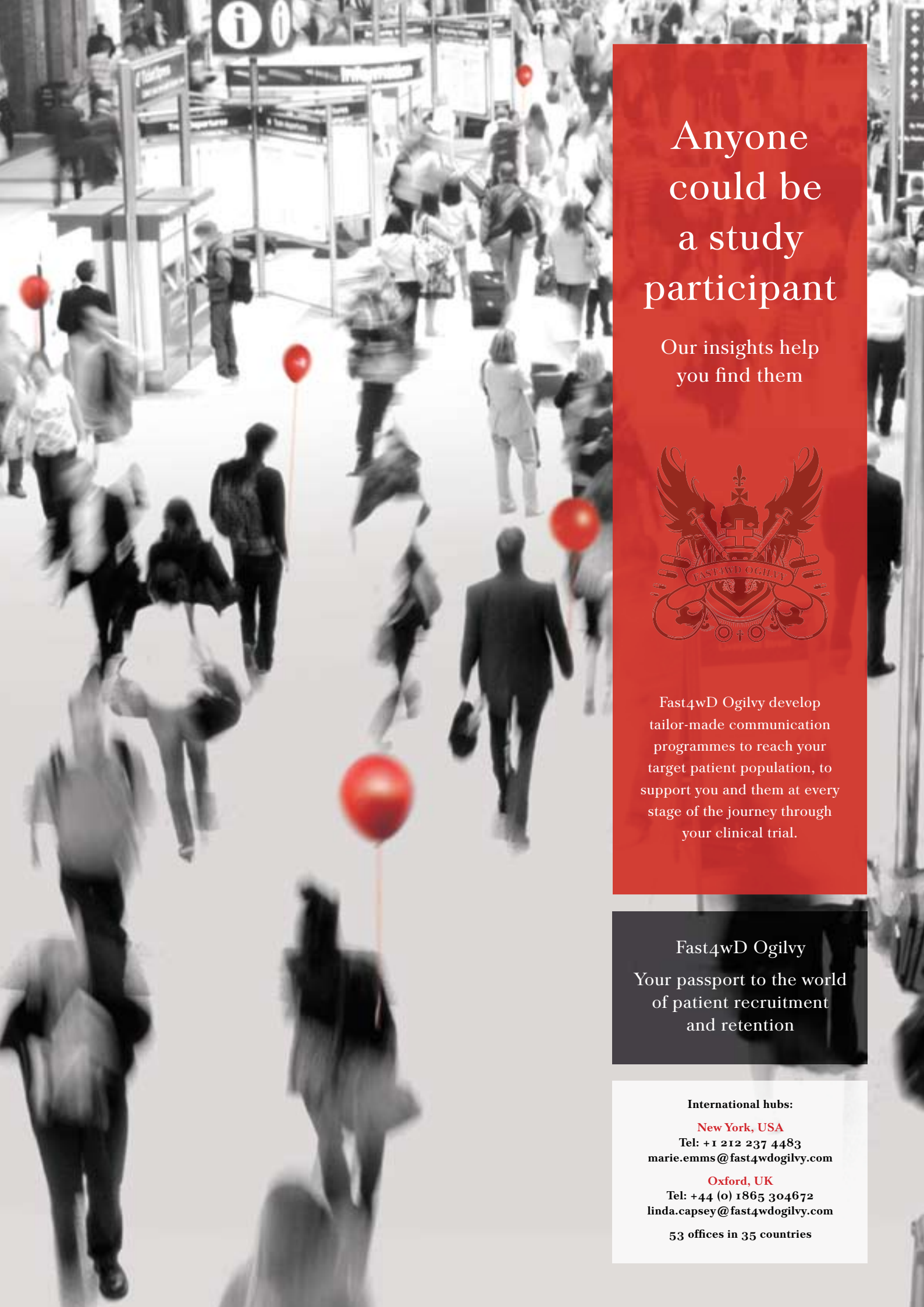
Processes in Need of Improvement

In response to the question, "In which of the following areas do you feel you need the most assistance in improving your success with your global patient recruitment initiatives?" the top three answers were: "country planning for patient recruitment", "site/country selection", and "patient recruitment training specific to a given indication/patient audience." Figure 1 shows the ranking of the most important areas for recruitment assistance for both audiences.

Figure 1. Cumulative Ranking of Most Important Areas for Recruitment Assistance



The variation in the answers is of key interest. For sponsors, country planning is a pressing recruitment consideration for many reasons, not least of which is that clinical study leaders are responsible for overall enrolment performance. If study leaders can provide effective recruitment plans customised by country, they will position their country managers and sites for success. On



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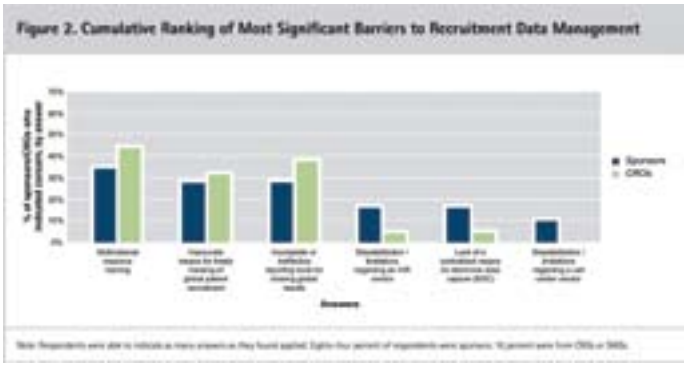
the other hand, CROs generally have responsibility for managing monitors and sites, and one of their greatest concerns is ensuring effective training specific to a given indication and patient profile. Providing this type of support to their sites empowers site staff to appropriately identify, approach, and consent the ideal patient population. Similarly, site/country selection for a global trial is more of a concern for sponsors than CROs because it is tied to recruitment success, as well as meeting business objectives.

The fact that these three functions are ranked so much higher than the last three (cultural adaptation, ethics submissions, and site/country manager support) indicates the increased recognition among these audiences of the need for effective planning and start-up processes to set the stage for successful patient recruitment efforts. Identifying and selecting the right countries and sites for a study is integral to ensuring enrolment performance at projected levels of need. Customising recruitment plans by country acknowledges the diversity of factors that influence recruitment, including regulatory environment, healthcare structure and reimbursement system, treatment patterns, and alignment of patient and physician motivation with the study's goal, among other issues. The focus on patient recruitment training specific to a given condition and patient type reveals a growing understanding that "one size does not fit all."

In short, the responses to this question indicate that sponsor and CRO leaders recognise the complexity of the global patient recruitment function, and the necessity of investing in the planning processes that form the foundation for implementing a successful patient recruitment campaign.

Managing Patient Recruitment Data

Sponsors and CROs followed the same split in answering the question, "In managing your recent global patient recruitment programmes, what has been your primary difficulty related to data management?" Figure 2 shows the ranking of the most significant barriers to recruitment data management for both audiences.



Clearly the greatest concern here for both sponsors and CROs is training multiple audiences on recruitment data management resources. Technological capabilities and access can vary significantly in different countries, making the top of the list of concerns for ensuring effective use of these systems for entry of recruitment data. CROs may be particularly concerned as they often provide the technology tools and training on behalf of the sponsor. Additionally, tracking and reporting on recruitment performance data is of equal concern to both sponsors and CROs. Both are facing a lack of timely tracking and complete reporting for sharing global results. This may be an indication that the tools in use are inadequate or ineffectively used – or both. Thus, the identified gaps point to a need for standardised tools and more efficient processes for rollout and implementation of recruitment technology training.

Interest in Enhancing Recruitment Tactics

Both audiences answered in a similar fashion to the question, "Which global patient recruitment tactics are of most interest for improvement?" The spread of answers was more balanced than in other questions, as shown in Figure 3.

These responses indicate fairly strong interest in improving development and implementation of recruitment tactics to support enrolment efforts. The top three answers for each group focus on materials and messaging for key audiences – patients and physicians – indicating an interest in supporting the investigative sites, the place where "the rubber hits the road" for actual randomisation. For sponsors, the number one interest was for effective study branding, which again indicates study leaders focus on the big picture of recruitment – in this case, to convey a strong study identity across countries and audiences.

Implications of the Research

The findings of this survey reflect sponsor and CRO concerns around patient recruitment that correlate closely with the increasing complexity of the global clinical trial enterprise. The results also suggest a growing recognition that simply adding "fast-enrolling" countries to a global trial is not a guarantee to achieve enrolment. Rather, responses seem to indicate that the overarching barrier to effective global patient recruitment is the current patchwork approach. Rather than establishing a recruitment strategy across countries before the study starts, leaders rely on each country's representatives to solve recruitment problems, often after enrolment is lagging. The solution would seem to be to institute standardised approaches to patient recruitment processes that can be integrated into all study planning and implementation processes, but that still leave room for customisation by the differing requirements of each country. An analysis of the key survey responses reveals three major concerns to which we can apply this solution.

Patient Recruitment-Related Training

Sixty-seven percent of CRO respondents and 35 percent of sponsors indicate patient recruitment training specific to an indication and a patient audience as the area where they most need assistance: in managing recruitment data, both groups' top concern was multinational resource training.

Effective training hinges on content and the delivery process. It is important for sponsors and CROs to have a strategy for patient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recruitment training that includes both factors. Patient recruitment processes have been refined into a body of knowledge, a discipline unto itself. This discipline can be drawn on to shape a standard curriculum that can then be modified by specific protocols as needed. There are technological tools on the market that can provide the kind of detailed data for recruitment performance reporting that sponsors and CROs need, but are most efficacious when incorporated into the overall training programme. Figure 4 shows one example.

Figure 4: Example of Standardising Recruitment Training Phase III Oncology Study.

(Second-Line Metastatic Treatment)

BBK Worldwide worked with the sponsor to design patient recruitment training for monitors and study managers. All participated in an initial workshop and a series of three webinars. Fifty percent of the participants received the Essential QuickTrainerSM, a standardised online patient recruitment course, and 50 percent did not (the non-supported group). Ninety-three percent completed the online course. The results: the non-supported group had an average enrolment rate of one patient every four months; the supported group had an average enrolment rate of one patient every three months – a 24 percent difference in performance.

Communicating with Patients and Physicians

Survey results indicate a need for better communications between those conducting the study, and the sites and patients who participate. The high ranking of the need for communications materials to support study enrolment points to the understanding that communicating well with these audiences leads to enrolment success. Sponsors and CROs are recognising that the support of a studywide communications programme, with messages that address and support – and in some cases, even articulate – the motivations of patients to enroll and of physicians to refer to the trial, is crucial to the trial's success. Figure 5 shows examples of standardised communications to patients and to referring physicians.

Examples of Standardising Patient and Physician Communications

Phase III Bipolar I Disorder Study (Paediatric) – Patient Communications

To enroll this three-country, 40-site, 190-patient trial, BBK Worldwide designed a study identity (brand) and messaging that would appeal to a difficult-to-enroll population – children and adolescents with bipolar I disorder. The campaign successfully motivated the three key target audiences and led to enrolment success: 1) for parents, it presented a portrait of their child that motivated them to seek help; 2) for patients, it expressed what they were feeling in a way they could not articulate for themselves; and 3) for physicians, who were enthusiastic about the materials, it energised their efforts.

Phase I/II Pompe Disease Study (Neonatal) – Physician Communications

Pompe disease is so rare that most neonatologists, neurologists, and paediatricians have never heard of it, and a paediatric neurology specialist may not see a single case in an entire career. Although this was a five-nation, eight-site study, patients could be recruited from anywhere around the globe because the sponsor would pay for travel. BBK Worldwide designed a referral request mailing. Materials included a compelling brochure that reminded physicians to "rule Pompe out early" whenever a patient exhibited symptoms that might be Pompe disease. BBK's innovative programme helped the sponsor enroll this landmark clinical trial – once thought unenrollable – ahead of projection.

Tracking and Reporting on Recruitment

With essentially equivalent responses, sponsors and CROs indicated inaccurate tracking of recruitment and ineffective reporting tools as two of the top three concerns for recruitment data management. Most clinical trial technology systems are focused on clinical data capture; very few are built to capture, analyse, and report specifically on recruitment data.

Sponsors and CROs recognise the importance of recruitment data in the planning stages, during the actual recruitment period, and through to randomisation. But without a flexible technology platform for standardising recruitment management, tracking, and reporting of that data, study leaders lack a critical resource to monitor recruitment performance at the site and country level by aggregating site results.

Example of Standardising Recruitment Data Tracking Metastatic Breast Cancer

For this five-country, 75-site study, BBK Worldwide conducted country research and developed recruitment plans and tools with which clinical research associates (CRAs) could provide enrolment support to their sites. First, BBK assessed sites for their recruitment capability, developing specific plans for each site to ensure effective recruitment activities. CRAs could then monitor their sites' progress in implementing recruitment plans through TrialCentralNetSM, BBK Worldwide's recruitment data management system. The result was strong and steady recruitment throughout the enrolment period that achieved the target goal right on time.

Closing Thoughts

The past few years have seen the clinical trial industry begin to adopt basic recruitment practices in a more consistent manner. The tools now exist to create standard operating procedures to ensure that recruitment considerations are built into the study infrastructure. This survey suggests that a more extensive application of the best recruitment practices is needed. Beyond the three specific areas identified in the implications section, the following broad recruitment categories can be broken into processes and standardised for a global study. Again, standardisation does not preclude customisation by country or region where necessary.

Study Start-up – Country selection, site selection, and understanding patient motivations to participate in the study all benefit from an objective recruitment-focused analysis. This is in addition to any other current standard analyses conducted by the sponsor (infrastructure, cost, feasibility, etc.), which leads to concrete plans for implementing appropriate recruitment efforts.

Recruitment Strategy – Determining recruitment strategies depends on institutionalising an understanding of patient and physician motivations for participating in or referring to a study – and they vary for every protocol. Understanding the audience's motivations guides the scope of the recruitment campaign and the range of tactics necessary for reaching enrolment on time. When these motivations are not parallel to the scientific goal of the study, recruitment tools aren't likely to overcome this challenge – focusing on country or site selection may be more productive.

Recruitment Tracking and Reporting – Platforms for standardising recruitment management, tracking, and reporting are all available and can contribute measurably to recruitment success. Supported by a robust recruitment technology system, data on enrolment shortfalls, deviations, and delays – and myriad other problems – can be captured, analysed, and corrected early on and monitored throughout the entire enrolment process to help sites achieve on-time recruitment.

There are many drivers for the globalisation of clinical trials beyond enrolment delays in the major markets. Emerging world markets are opening to new medical treatments and the research that creates them, and research-sponsoring companies are developing more and better medicines to meet the need. Meanwhile, patients around the world are becoming more educated about healthcare and seeking broader options for treatment. Even if going global were a panacea for on-time clinical trial enrolment, the continuing sophistication of all the world's healthcare consumers would soon demand harmonisation of ethical communication processes around clinical trial education.

The lessons learned about recruitment delays in more developed clinical trial countries can inform those beginning to arise in emerging markets. Right now, although recruitment rates may be higher in some countries, barriers to start-up are also higher. Roadblocks to on-time study enrolment will continue to crop up. Incorporating the most advanced recruitment methods into the standard operating procedures of clinical trial planning and implementation will facilitate the delivery of new medicines to all corners of the globe.. ●

Results and Analysis from a BBK Worldwide Survey of Sponsor and CRO Representatives.

References:

1. Glickman S. et al, "Ethical and Scientific Implications of the Globalization of Clinical Research," New England Journal of Medicine, Vol. 360 (8) (February 19, 2009): 816-823.
2. Outlook 2007, Tufts Center for the Study of Drug Development, 2007.
3. 2008 State of the Clinical Trials Industry: A Sourcebook of Charts and Statistics, CenterWatch, 2008.

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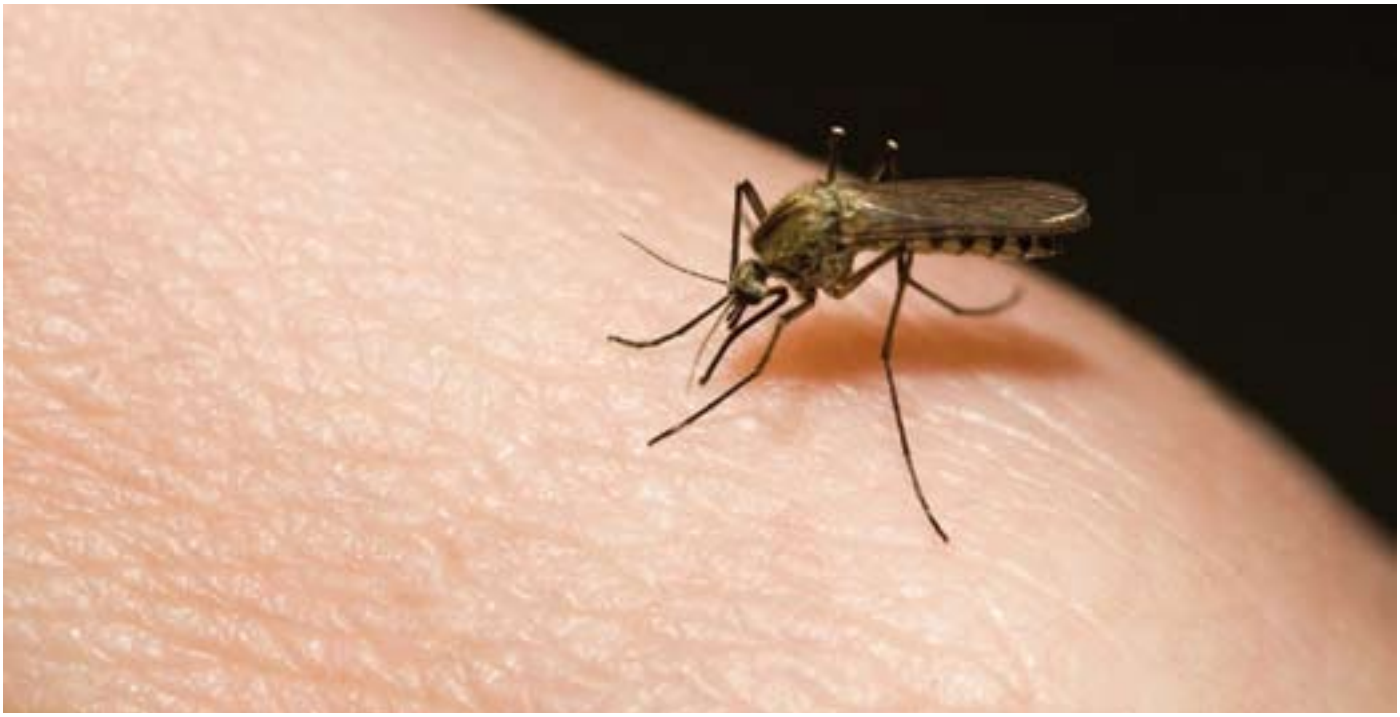
Roll Back Malaria in Africa: A Review, Ten Years After the Abuja Declaration

Malaria kills over two million people each year globally, and is a major threat to public health and economic development in Africa. An estimated 270 million clinical cases are reported worldwide each year, of which more than 80 % occur among children below the age of five years. Although considered a global public health problem, 95 % of global malaria deaths occur in sub-Saharan Africa. Despite being preventable and curable, malaria remains one of the most serious public health problems on the African continent. The disease has its claws firmly planted in the fabric of African life, where it causes untold suffering and impedes economic development. Reports indicate that it slows economic growth in African countries by 1.3 % annually, and that Gross Domestic Product (GDP) in African countries is 37 % lower than it would have been in the absence of malaria. In 1997 malaria cost Africa 2 billion US dollars.

A decade ago, on the 25th of April, 2000, heads of states and governments from 44 of the 50 most malarious countries in Africa gathered in the Nigerian city of Abuja for the *African Summit on Roll Back Malaria*, where they signed a landmark declaration that has come to be referred to as the *Abuja Declaration on Roll Back Malaria in Africa*. Here they rededicated themselves to the principles and targets of the *Harare Declaration* of 1997. They committed themselves to an intensive effort to halve malaria mortality on the continent by 2010, through implementing strategies and actions for Roll Back Malaria. The Summit was also attended by senior officials from each of the four founding agencies; WHO, the World Bank, UNICEF, and UNDP Africa, as well as other key partners like UNESCO, the African Development Bank, USAID, DFID, CIDA, and the French Co-operation. The summit, which concluded with the signing of the Declaration and a plan of action, reflected a real convergence of political momentum, institutional synergy and technical consensus on malaria in Africa and efforts towards its eradication. In this review, a summary of the strategies and an evaluation of the progress made thus far will be discussed. This review also briefly touches on what lies ahead with regards to malaria eradication on the continent as part of global efforts and strategy to eradicate malaria.

Strategies and Efforts for Malaria Eradication

To better appreciate the malaria situation in Africa today, it is important to take a look at the history of the disease, and previous global efforts for its control and eradication. In the mid-19th century, malaria had a global distribution and was endemic in most countries of the world, with close to 90 % of the world's population being affected. The first efforts to control malaria that showed promise started in 1945 with the use of DDT. In 1955, an intensive malaria eradication campaign was launched at the 8th World Health Assembly. Although the campaign was aimed at eradicating malaria from all countries at risk, no sub-Saharan African country was considered. The strategy involved primarily indoor residual spraying with DDT that had shown great results ten years earlier. This, coupled with timely malaria case management, produced by the late 1970s 37 malaria-free countries of the 143 with previously endemic malaria. None of these 37 countries was in Africa. Despite these small though vital gains, malaria eradication as a time-limited programme was found to be impractical, and the strategies shifted to long-term integrated programmes.



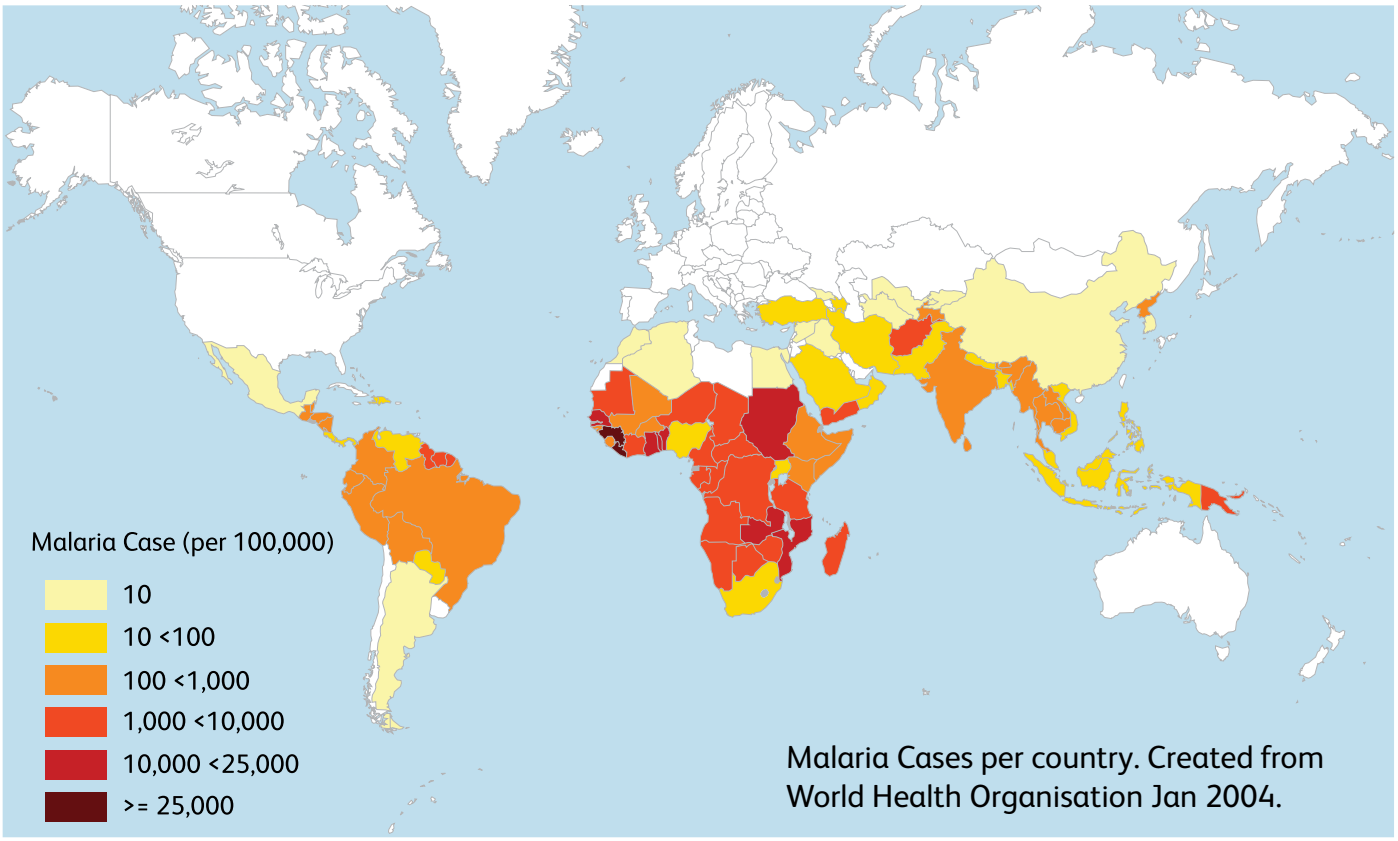
The concerted Global Malaria Eradication Campaign that had registered some successes was abandoned. This, together with several other factors, notably the increase in parasite and vector resistance to the anti-malarial drugs and insecticides in use at the time, led to the resurgence of malaria as a global public health problem of alarming proportions, especially in sub-Saharan Africa and south-east Asia, in the 1980s onwards. In 1992, the Global Malaria Control Strategy was launched to attend to the growing threat of the global malaria situation. This effort led to the creation of the Roll Back Malaria (RBM) Partnership in 1998, tasked to coordinate global efforts in combating malaria. These global efforts are also supported by the United Nations through the Millennium Development Goals (MDGs).

By the year 2000, over half a century into the history of scientific malaria control, too little had been done on the African continent in the form of a concerted effort to control the spread of malaria. The malaria death figures were growing each year, and the devastating effects of the disease were very evident in African life. As the African leaders might have realised prior to the Summit on Roll Back Malaria, this state of affairs owed itself more to an unspoken political neglect than scientific failure, evidenced, for instance, by the world's agreement to leave Africa out of the malaria eradication and control era of the 1950s to 1970s, and the dearth of research on malaria at the time. The political will, and by extension, the resources, had simply not been available to do better. The *Abuja Declaration* was therefore a sign that malaria was gaining political support from African leaders themselves, and that a concerted effort to control the disease was in the offing.

But of all the progress in the Abuja Declaration, the greatest was the recognition that Africa urgently needed resources to carry out malaria control effectively. This was reflected in two bold requests to western governments and the donor agencies; the first request was to cancel in full the debt of poor and heavily indebted countries of Africa in order to release resources for poverty alleviation, and the other was to allocate substantial new resources of at least one billion US dollars per year to Roll Back Malaria in Africa. International donors responded positively to the request for substantial new resources for malaria control. The World Bank pledged an additional 300-500 million US dollars towards malaria control in Africa. Similarly, the Canadian International Development Agency (CIDA) announced an additional 6.5 million US dollars over a period of five years towards Roll Back Malaria in Africa. On the side of the delegates, pledges and commitments were made, and a plan of action for achieving the goals and targets of the declaration was formulated with the following as priority areas;

- Disease management
- Provision of anti-malarial drugs and malaria control related materials
- Disease prevention
- Disease surveillance, epidemic preparedness and response
- Sustainable control
- Human resource development
- Research

Indicators for monitoring and evaluation as well as a framework for reporting were defined.



Malaria Cases per country. Created from World Health Organisation Jan 2004.

The Situation a Decade Later

Although the target is still far from being achieved, there are some successes registered in parts of the continent worth mentioning. According to the *WHO 2009 World Malaria Report*, Zambia, Rwanda, Eritrea and parts of Tanzania managed to reduce deaths from malaria among children below five years by 50% in the last ten years. The report also indicated that funding commitments from international donor agencies increased from 300 million US dollars in 2003 to 1.7 billion US dollars in 2009. Notable among these donors is the Global Fund, the US President's Malaria Initiative and the World Bank. Since its inception in 2002, the Global Fund (GF) has been making very bold steps in the fight against malaria through the distribution of over 100 million insecticide-treated nets (ITNs), distribution of artemisinin-combination therapy (ACT) drugs, and funding various other malaria control programmes. In 2008, the GF reported that it had distributed 46 million ITNs in 78 countries through its 146 programmes globally. Data from 20 African countries show an increase in the use of ITNs, with 16 of the countries tripling their usage since 2000. Although the use of ACTs has also increased in malarious countries globally compared to 2006, it still remains significantly low in most African countries. This is attributed to the cost of the therapies that many countries in Africa cannot afford. According to a recent report on Roll Back Malaria, an estimated 908,000 deaths have been averted in Africa since 2000, due to an increase in the number of people sleeping under an insecticide-treated bed net. Although this is a positive trend, the figure is still very low compared with the lives that are not saved. There is still a lot of work to be done to achieve the targets of the *Abuja Declaration* on Roll Back Malaria in Africa.

The Future

Despite the successes recorded on the continent over the past ten years, it is widely believed, and is indeed patently clear, that the fight against malaria in Africa is still far from being won. However, if the current favourable funding climate for malaria control is coupled with renewed political will and action, there is hope on the horizon. African leaders, policy-makers and scientists need to recommit resources towards malaria control. Political will needs to be followed up with vigorous action. Major reasons cited for the failures of the Malaria Eradication Campaign launched in the 1950s were political instability and technical challenges in delivering resources. Unfortunately, these are still major challenges today and could be attributed to the shortfalls of the *Abuja Declaration* targets. Although this was widely believed to be the boldest show of political consensus and will by African leaders to fight malaria on the continent, many countries performed dismally, and this was largely attributed to lack of political action. By 2006, although almost all countries had set up national malaria partnerships and collaboration programmes dedicated to controlling malaria, only a third had allocated 10% of their national budgets to health, and only one country had attained the targeted 15%. This was a huge contrast to, for example, the huge expenditures on defence in the same countries as reported by the Stockholm Peace Research Institute for the same period. Other political factors that can be imputed to this failure include conflict, corruption and inefficient institutions. Beyond the obvious effects, political instability and corruption discourage the vital funding needed for the control programmes. Without greater political will from African countries, many of the efforts will not yield much in terms of fighting malaria. It is therefore imperative that African governments build roads and health facilities, train health workers, formulate relevant and practical health policies, instigate mass mobilisation of communities, and foster accountability, to create a conducive socio-political environment that will go a long way in augmenting the fight against malaria and other diseases.

It is widely recognised that any attempt at malaria eradication

must be a long-term commitment that involves multiple interventions, disciplines, strategies and organisations. One of the means to develop important new tools critical to the eradication of malaria is through research. Malaria eradication will require a sustained, multidisciplinary research effort by multiple partners in Africa and across the globe. One of the trickiest issues with malaria is the shift in the disease patterns over the years. Many strains have become resistant to current treatments as has been the case over the last 50 or so years. Such changes in the patterns of the disease will require new interventions in the form of diagnostics, drugs, and ultimately an effective vaccine. It is therefore important to maintain a robust pipeline of new interventions that can substitute for failing ones. The challenge in this continues to be translation of the current basic information about malaria parasites, mosquito vectors and the human host into new intervention strategies. An example of this is how to translate the current knowledge of the genetic sequences of *P. falciparum* and *P. vivax* into better ways of blocking transmission or preventing and treating infection.

Finally the other challenge and hope for malaria control is continued and increased funding for the various control initiatives and programmes. According to the Roll Back Malaria Partnership press release in 2005, many countries can achieve the Millennium Development Goal of halving the number of malaria deaths by 2015, but only if the world remains committed to providing the money needed to ensure universal coverage of malaria control interventions. In light of this, the Bill and Melinda Gates Foundation in the last quarter of 2007 convened a malaria conference in Seattle, Washington, USA, during which Bill Gates made a call for the eradication of malaria. This call has generated a lot of debate among public health experts and stakeholders, and the general public. Some feel this is an audacious goal, considering that the tools to be used in the eradication do not yet exist. However, Dr Regina Rabinovich, the Head of Infectious Diseases at the Bill and Melinda Gates Foundation, believes that with more money, better health systems and probably a vaccine, the undertaking can be realised in the long term. ●

References:

1. Roll Back Malaria: Progress and Impact series report, April 2010
WHO. World Malaria Report 2009.
2. WHO. The Abuja Declaration and the Plan of Action. An extract from the African Summit on Roll Back Malaria, Abuja, 25 April 2000 (WHO/CDS/RBM/2000.17).
3. Butler D (2004) Global Fund changes tack on malaria therapy. Nature 429
4. Global Fund to Fight AIDS, Tuberculosis and Malaria. Commitments and disbursements. 2009.

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Dimebon: Effective or Not Effective for the Treatment of Alzheimer's Disease

Two years ago, in 2008, Dimebon was considered a promising new medicine for the treatment of Alzheimer's disease. So, has it been confirmed or not?

Dimebon blocks H1-receptors, and partly blocks M-cholinoreceptors and 5-hydroxytryptamine receptors. It acts with antihistaminic, antiserotoninic, M-cholinoblock, local anaesthetic and sedative effects. Dimebon helps to prevent anaphylactic shock, decrease pruritus and the intensity of local exudative appearances, and decrease penetrance of vessels. The antiallergic effect shows 2-3 days after starting the treatment. Dimebon was used in the Soviet Union mainly as a medicine against allergies for a short period, and then was withdrawn from the market due to side-effects.

New Life of Dimebon

In 2008, Dimebon was proposed by Medivation as a new treatment agent for Alzheimer's disease as a cholinesterase inhibitor, like the standard Alzheimer's disease treatment drug group such as donepezil, galantamine, and rivastigmin.

Dimebon was announced as an orally-available, small molecule compound that has been shown to inhibit brain cell death in preclinical models relevant to Alzheimer's disease and Huntington's disease, making it a potential treatment for these and other neurodegenerative conditions. In 2009 Medivation and Pfizer decided to collaborate on the Phase III programme in Alzheimer's disease, Huntington's disease development and regulatory filings in the United States.

In March 2010 the pharmaceutical company Medivation experienced a severe stock drop in the wake of the news that its experimental drug Dimebon (or latrepirdine) used for the treatment of Alzheimer's disease does not show significant efficacy. The consequences of failed trials are:

- stock drop of 67 %
- fallback in drug treatment of Alzheimer's disease

The investigative anti-Alzheimer's treatment developed by Medivation and Pfizer failed to meet "efficacy endpoints" in late-stage Phase III trials. Moreover, no statistically significant improvements relative to placebo were achieved on the co-primary endpoints. The efficacy of the drug was measured by cognition and global function.

Probable Theoretical Explanation of Dimebon Failure

Results from the first pivotal trial of Dimebon in Alzheimer's disease showed that patients treated with Dimebon experienced statistically significant improvements compared to placebo in key aspects of the disease - memory and thinking, activities of daily living, behavior and overall function. Dimebon's benefit over placebo continued to increase throughout the 12-month treatment period. The results of the study were published in the July 19, 2008 issue of The Lancet, "Effect of Dimebon on cognition, activities of daily living, behavior, and global function in patients with mild-to-moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled study".

Let's consider the potential efficacy of Dimebon for Alzheimer's disease based on this publication.

Mechanism of Dimebon's Action

It blocks NMDA receptors and inhibits mitochondrial permeable transition pores opening. The different mechanism of action present was registered with the Russian Regulatory Authorities: "Dimebon blocks H1-receptors, partly M-cholinoreceptors and 5-hydroxytryptamine receptors". It seems that Dimebon was transferred to another pharmacological group without enough scientific material, because a lot of significant information about Dimebon is missing. For example, no information is available regarding drug bioavailability, metabolism, half life, and excretion. It is unclear now how to explain the antiallergic effect of Dimebon based on the "latest" action mechanism, because no "antiallergic" receptors are mentioned in the "new" mechanism of action.

Interaction with Other Psychoactive Drugs

The next point which should be covered is that Dimebon perhaps showed high efficacy in the study published in the Lancet because other psychoactive drugs, for example barbiturates, were allowed during the study. Other pharmaceutical companies, for the most part, strictly prohibit using such medicines starting from the wash-out period and later during the screening phase, baseline, treatment and follow-up. It is required not only to prove the efficacy of the investigational product, but also to find possible short-term and long-term adverse events. We can also conclude that interaction took place based on analysis of adverse events – depression. According to the packing list of Dimebon, depression can only take place if interaction with other psychoactive drugs has occurred (see Appendix 1). Additionally, some obvious and common adverse events such as numbness of mouth mucous membrane, drowsiness, and decrease of attention concentration ability were not mentioned in the article.

The Study Period

Finally, it is doubtful that 183 patients could be randomised to the study for such a short period. We can conclude again that subjects with other kinds of psychiatric disease, not just Alzheimer's disease, were included in the study.

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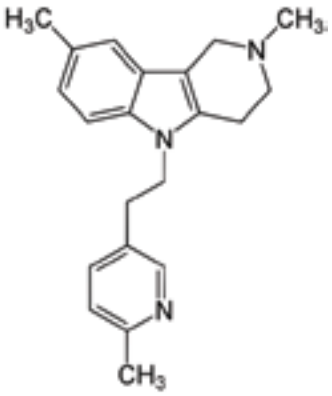
Medivation and Pfizer failed to meet "efficacy endpoints" in late-stage Phase III trials. Moreover, no statistically significant improvements relative to placebo were achieved on the co-primary endpoints. The efficacy of the drug was measured by cognition and global function. Despite the results, Pfizer and Medivation initiated two Phase III trials of Dimebon in patients with moderate-to-severe Alzheimer's disease (Pharmacy Drugs on June 25th, 2010).

The CONTACT study will assess as primary endpoints the potential benefits of adding Dimebon to ongoing treatment with donepezil HCI tablets, the leading AD medication worldwide, on neuropsychiatric symptoms and activities of daily living. The CONSTELLATION study will evaluate as primary endpoints the effects of adding Dimebon to memantine HCI, another standard of care, on cognition, memory and activities of daily living.

About the CONTACT Study

This Phase III randomised, double-blind, placebo-controlled study will enrol approximately 600 patients with moderate-to-severe AD and neuropsychiatric symptoms at approximately 75 sites in Europe and South America. Patients who are already taking donepezil will be randomised to also receive either Dimebon 20 mg three times daily or placebo, for six months.



Structure of Dimebon

The CONTACT study is designed to assess patients' behavioural difficulties and their ability to perform routine activities of daily living. Behaviour will be measured by the Neuropsychiatric Inventory (NPI), while self-care and daily function will be measured by the Alzheimer's Disease Cooperative Study - Activities of Daily Living (severe) (ADCS-ADLsev). Secondary endpoints include measures of cognition, memory, global function, pharmacoeconomic impact, quality of life and safety and tolerability.

About the CONSTELLATION Study

This Phase III randomised, double-blind, placebo-controlled study will enrol approximately 570 patients with moderate-to-severe AD at approximately 80 sites in the United States, Canada and Europe. Patients already taking memantine will be randomised to also receive either Dimebon 20 mg three times daily or placebo, for six months.

The CONSTELLATION study will evaluate the potential benefits of adding Dimebon to ongoing memantine therapy on cognition, memory and activities of daily living. Cognition and memory will be measured by the Severe Impairment Battery (SIB), while self-care and daily function will be measured by the Alzheimer's Disease Cooperative Study - Activities of Daily Living (severe) (ADCS-ADLsev). Secondary endpoints include measures of cognitive and behavioural symptoms, global function, resource utilization, quality of life, safety and tolerability.

To sum up, we cannot now conclude that Dimebon is an effective medication against Alzheimer's disease. We must await the results of further clinical trials with Dimebon.

Appendix 1 Information on packing slip of medicine for treatment of allergic diseases, Dimebon, registered in Roszdravnadzor, regulatory authority of the Russian Federation.

Dimebon:

International nonproprietary name:
Dimethylmethylpyridinylrthyltetrahydrocarbonyl

Pharmacological group:
H1-receptors blocker

Description of acting agent:
Dimethylmethylpyridinylrthyltetrahydrocarbonyl

Drug formulation:
Tablets; tablets for children

Mechanism of action:
Dimebon blocks H1-receptors, partly M-cholinoreceptors and 5-hydroxytryptamine receptors. It acts with antihistaminic, antiserotoninic, M-cholinoblock, local anaesthetic and sedative effects. Dimebon helps to prevent anaphylactic shock, decrease pruritus and the intensity of local exudative appearances, and decrease penetrance of vessels. The antiallergic effect shows 2-3 days after starting the treatment.

Indication:
Allergic palpebral diseases, conjunctivitis, pollinosis, urticaria fever, hay fever, food and cosmetic allergy, medicine allergy, angioedema, atopic dermatitis, atopic dermatitis, allergic and inflammation eyes diseases, burn toxemia, allergic reactions: edema, pruritus and eczema, reactions, related to stings.

Contra-indication:
Hypersensitivity, pregnancy, lactation period.

Adverse Events:
Dry mouth, numbness of mouth mucous membrane, drowsiness, decrease of attention concentration ability.

Mode of administration and doses:
Per os, irrespective of taking food, for adults – 10-20 mg 2-3 times per day, duration depends on severity of symptoms – 5-12 days. Daily doses for children: before 1 year old - 5-7.5 mg, 1-2 years old - 5-15 mg, 3-5 years old - 7.5-30 mg, older than 5 years - 20-40 mg; 2-3 times daily.

Special instructions:
Administration during pregnancy is possible only in special circumstances. During treatment period caution is required while driving and engaging in potentially dangerous activities, or activities requiring concentration and rate of psychomotor ability (during the treatment period people should not perform such activities).

Drug interaction:
The depressant action on CNS will be exacerbated with simultaneous administration of hypnotic, anxiolytic, antidepressant, antipsychotic and narcotic analgesic drugs.

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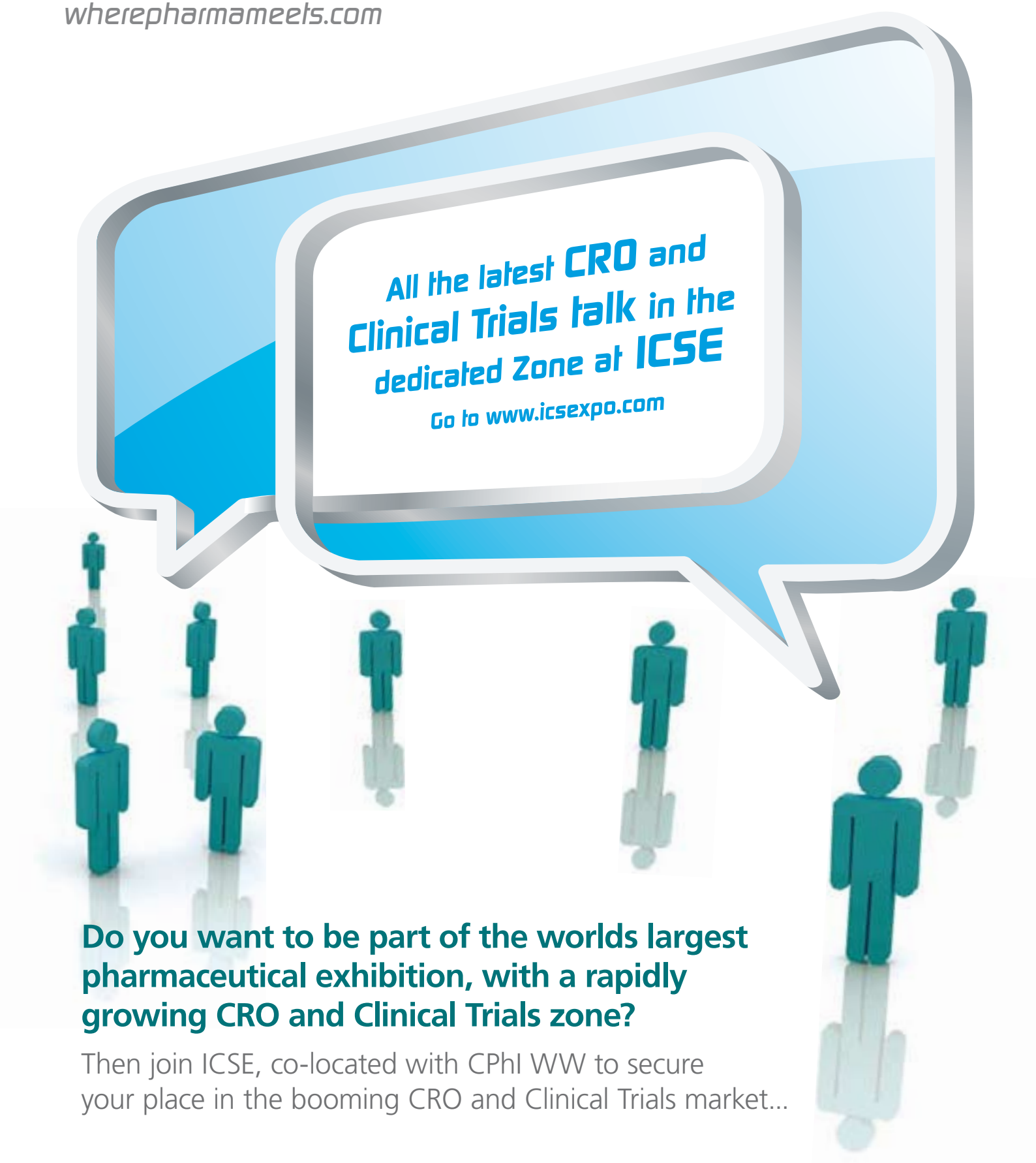

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Electronic Patient Reported Outcomes: The Future of Patient-Centred Data in Global Clinical Trials

As collecting data directly from patients has become a common practice in clinical trials on a global level, Electronic Patient Reported Outcomes (ePRO) have proven to be a valuable option for data collection. This article discusses trends of patient-centred data and the benefits and challenges of the use of ePRO.

Trends in Global Clinical Trials

In medical practice, an evolution occurred that refocused medicine to the patient's point of view (1). Historically, medical care was centred on clinicians, but gradually clinicians came to realise that the patient's point of view often advanced the course of care and led to better healthcare outcomes. They began to understand that while scientific evidence is important, each patient has unique circumstances, needs, and preferences which influence treatment effectiveness. Through this shift to patient-centred care, clinicians found that having the patient involved in the process of care significantly improved adherence to the treatment plan (2). Likewise, the pharmaceutical industry recognised this shift in medical practice and began adapting such practices into clinical trials. Today, patients are being increasingly viewed by the industry as the end-consumer rather than the clinician. Consequently, clinical trials are more focused on the patient as a principal factor in the success of studies. Placing patients at the centre of research is essential because it facilitates filling gaps in the evidence that are needed to make informed decisions relating to drug development and commercialisation of pharmaceutical products (3).

The shift to patient-centred research and medicine brought about the significance of Patient Reported Outcomes (PROs) in clinical trials. As such, PROs are now a central focus within clinical trials for measuring treatment efficacy and safety, as well as providing data for clinical trial endpoints to support regulatory submissions. Unlike laboratory tests that require interpretation from a secondary source such as a clinician, PRO measures come directly from patients to provide their insights throughout the course of clinical trials. Therefore, PROs allow trials to be patient-centred since they provide that direct connection of the patient to the trial. Moreover, following the launch of clinical products, PROs have become increasingly important in helping better position and differentiate drugs in the marketplace, gain product admission into formularies, and subsequently pave the way for reimbursement – three pillars of product commercialisation success.

Another predominant trend is to conduct clinical trials worldwide, which can make the collection of PROs challenging. PROs initially were collected via paper, which brought about several issues, as paper data collection has several flaws. Fortunately, there have been vast developments and improvements in technology, allowing for the advancement of electronic means for the collection of PRO data. Electronic Patient Reported Outcomes (ePROs) now exist as an alternative to paper, thus offering a suitable solution to effectively and efficiently collect PRO data on a global level. Table 1 shows how ePRO has made dramatic improvements in data quality over the use of paper. Furthermore, studies have consistently shown that patient compliance for completion of PROs and data quality are significantly higher when PRO assessments are administered electronically (4, 5). Essentially, PRO endpoints must be viewed and treated as any other clinical trial endpoint, therefore high data quality and compliance is extremely important.

In addition to providing superior quality data and higher patient compliance for PRO completion, ePRO provides several advantages over paper PRO in global clinical trials. Multiple modalities exist for the collection of ePRO, such as Interactive Voice and Web Technology systems (IVR/IWR), hand-held devices/personal digital assistants, mobile technologies, and other electronic data capture systems. Having multiple modalities available affords sponsors/investigators the choice to implement one or more of these technologies in congruence to the clinical, logistical, and financial requirements of specific trials.

ePRO systems are very helpful in the management of three critical objectives of any clinical trial: successful patient recruitment, retention, and treatment adherence. Recruiting patients is a pivotal factor in its success, and a leading reason that most clinical trials are delayed (6). While ePRO cannot physically bring patients into a trial itself, it can be very helpful with the identification and tracking of patients, particularly when ePRO is collected on Interactive Voice and Web Response Systems (IVR/IWR), which are typically used for recruiting, screening, enrolling, randomising, and tracking patient visits in clinical trials. In these cases, patient management data remains in one system and enhances study reporting.

ePRO technology is also valuable with regard to patient retention, by keeping patients engaged throughout the trial. As in medical practice, professionals involved in clinical trials have also found that gaining insights from patients keeps them interested in treatment and increases treatment adherence. Beyond collecting ePRO data from patients, functionalities available in ePRO systems further enhance retention through sending various types of reminders, alerts, and messages to patients to inform them of upcoming study visits and milestones. These reminders/messages can also be extended to aid in treatment adherence by reminding patients to take their medicine, fill out their diary, and so on. With these functions and features that ePRO systems employ, not only does ePRO allow for effective data collection and management, but it also aids in overall patient management for global clinical trials.

Challenges of Implementing ePRO:

While ePRO is an optimal way of collecting PRO data, several challenges exist in its implementation during clinical trials. The first is actually getting sponsors/investigators to make the decision to use ePRO, since many PRO instruments are still administered in a traditional paper and pencil type of format (7). Even though paper PRO clearly has its downfalls, some sponsors/investigators are reluctant to implement ePRO in their trials due to fears of slowing study start-dates, incurring additional costs, and spending time on validating paper instruments for use in electronic data capture tools, such as IVR/IWR. However, it is now clear that the extra work and time associated with data input, querying, and management functions of paper PROs leads to increased costs and extended lengths of time spent on the back end of the study. By contrast, electronic data capture modalities actually reduce costs and timelines by eliminating these data management functions, thereby reducing study timelines. Another reason for the continued use of paper PRO is that there are significant numbers of PRO assessments that have been validated only for the use of paper-based data collection, as many PRO instruments were originally created on paper. This challenge is easily overcome by utilising instrument developers and researchers to convert and validate paper-only PROs for use in electronic formats such as IVR/IWR, hand-held devices, and other data collection tools. Fortunately, there are a variety of vendors that manage these tasks in a cost-effective and timely manner.

Paper	ePRO
Patients can enter erroneous data (i.e., easily fill in out-of-range values; make up their own responses by writing in the margins; make contradictory responses throughout the PRO)	Logic can be programmed to prevent erroneous entries and contradictory responses
Nearly impossible to verify the exact time that a patient entered data into a diary. Lapses of time between when patient completes data entries and when they are accessible for investigators/ sponsors	Data entry is time-stamped and becomes immediately available for investigators and sponsors for decision-making purposes and analysis
Site/study staff can easily corrupt data through secondary data entry, resulting in poor data in database	Direct data entry to eliminate/reduce data entry errors by site/study personnel
Data susceptible to loss (i.e. lost in the mail, misplaced, etc.).	Direct data entry to eliminate potential of lost or missing data
Burden on patient with having to do the extra step of mailing or hand-delivering	Direct data entry reduces the patient burden to deliver completed PROs
Storage of paper data can bring about loss and damage of data due to water, tearing, deterioration, fire, etc.	Storage of data in databases with backups prevents loss of data
Patients can easily skip questions and/or pages	Hard edits to eliminate patients from skipping items or pages
Patients can forget and fail to complete assessments and/or entries	Reminders to patients can be sent in real time. Alerts can be sent to study staff regarding patient non-compliance

Table 1: Paper versus ePRO

Understanding and navigating various regulatory issues on a global scale also presents challenges to the successful implementation of ePRO and patient-centric clinical trials. Study sponsors must remain compliant with the requirements and expectations of the individual international regulatory agencies relating to patient confidentiality of ePRO, level of psychometric testing, PRO instrument documentation, and other matters regarding the implementation of ePRO. Given the relative newness of PRO research, requirements and expectations of regulatory agencies can sometimes be unclear. To help remove some of the uncertainty for the United States, the Food and Drug Administration (FDA) has issued a PRO guidance document to assist the industry in the use of PROs in medical product development and to support labelling claims (8). Since some of the areas and issues may not be covered in detail in the guidance, it is important to communicate with the FDA to identify what would be acceptable and appropriate for the given clinical trial. To this extent, if the regulatory requirements of a given region outside of the US are unknown, it would be necessary to communicate with that particular region's regulatory agency during the planning phase of a trial. Since not meeting regulatory requirements/expectations can have negative consequences on the usability of the trial results, communication with these agencies prior to the trial's start is critical.

Conducting trials globally also presents the challenge of managing several different languages and cultures. Since patients have to directly respond to PRO assessments, it is important that the ePRO instrument either currently exists in certain languages or is properly translated to ensure consistency of results across patient populations. Translating PRO instruments can sometimes be challenging for several reasons. It is necessary to accurately translate along a number of dimensions: 1) appropriate content and intended meaning, 2) understandability within the context of the language, 3) proper accounting for different language dialects, and 4) meeting the translation expectations and requirements (i.e. forward translation, backward translation, level of psychometric testing) of the different international regulatory agencies. Careful selection of experienced vendors helps to overcome these hurdles. In short, proper translation requires sponsors to conduct research on the intended instrument, understand the regulatory requirements, and sometimes utilise translation experts to ensure reliability and validity of the instrument.

Understanding the technology infrastructures in various countries and study personnel preferences for certain types of technologies is crucial to ensure success of a global ePRO study. Pharmaceutical professionals, particularly those in charge of study design and protocol development, must understand the various technology capabilities of particular countries on a macro level, and specific clinical trial sites on a micro level. They must take into consideration the preferences and usage patterns of particular technologies (especially the preference for mobile technologies in emerging regions) from nation to nation and site to site, as well as within age groups and other demographics. Some areas have advanced telephony systems and capacity, allowing for easy-access

to both landline and mobile phones, but others may not. Some regions may have advanced internet infrastructures in place that deliver high-speed web services, while others do not. Users in some regions prefer to use the internet/web to manage patients, drug products, and other aspects of a trial, while users in other regions may prefer mobile phones or IVR. Conducting proper research and making active preparation for these types of factors is crucial in generating high quality data from patients, sites, and investigators worldwide.

Study designers must also be aware of patients' and sites' access to certain technologies. Access to computers, mobile devices, and other electronic data capture tools vary widely from site to site and from household to household. Often, study nurses and coordinators on sites share computers and face obstacles to making long distance or foreign toll-free calls. Yet these challenges are easily overcome every day during clinical trials, and pale in comparison to some of the issues sponsors confront using proprietary hand-held devices to collect patient data. In global trials, such devices must be distributed worldwide, which requires understanding specific countries' customs procedures and regulations, as well as the specifications and standards for electricity provision in different areas. Sponsors/investigators need to recognise these different technology infrastructural and access-related challenges when choosing the appropriate ePRO modality/ies for their clinical trial.

Finally, in any given clinical trial, whether conducted globally or locally, compliance of data completion will always remain a concern and challenge. The goal is getting patients to complete the required ePRO assessments per protocol. To achieve this objective, sponsors/investigators and ePRO systems need to optimise the user experience for the patient. In a literature review that explored non-compliance of data completion in ePRO trials, patients reported that the time to complete ePRO tasks was the top reason for non-compliance (9). In light of such data, sponsors/investigators must implement ePRO data collection methods that are user-friendly, reasonable in length, and are not burdensome on patients. Patients also reported that they were non-compliant due to system challenges and failure to remind them to complete their ePRO tasks. These findings support the notion that it is essential for ePRO developers to create quality systems that have no or very limited system issues, consistently deliver working reminders to patients, and send alerts to sites notifying them of non-compliance. Such reminders can be delivered via SMS/text, email, phone calls, or other ways requested by the patient or site.

Data completion compliance is also directly associated with patient satisfaction. In literature that assessed patient satisfaction in the use of paper versus ePRO assessments, the most common patient explanation for favouring ePRO was that it was easy to use (10). Patients stated that ePRO was more up-to-date, novel, eco-friendly, portable, accurate, convenient, informative/helpful, and faster to complete than paper PRO instruments. Moreover, patients felt that they were being more closely monitored and received higher quality treatment with ePRO because data was reported in real time, and could be responded to more quickly by site professionals during the trial. These findings show that patients value the experience of using ePRO and further demonstrate how technology can be applied to improve the patient's journey through the clinical trial.

Conclusions: Thinking of the Patient:

Based on lessons learned from medical practices, ePRO is now being widely applied to support global clinical trials and the marketing of drugs worldwide. While challenges exist for implementing PROs and gaining patient insights during global clinical trials, ePRO enhances the success of such efforts by supporting the patient's journey throughout the study. The wide range of ePRO features and functionalities not only deliver the collection of quality PRO data, but also support high levels of PRO compliance, patient management, treatment adherence, and patient retention during clinical trials. Following product launches, ePRO helps ensure the commercial success of products in the global market by providing key insights that differentiate one product from another, improve prospects for formulary admission, and pave the way for product reimbursement. The key to success on both a clinical trial and commercialisation basis is the ability of the sponsor and its vendors to design and implement user-friendly ePRO data collection tools that enhance patient satisfaction. With multiple electronic modalities available to achieve that strategic objective, sponsors are now rapidly adopting ePRO as a favoured tool for collecting PRO data and patient insights on a global scale. ●

References:

1. Laine, C. & Davidoff, F. Patient-centered medicine. A professional evolution. JAMA. 275(2), 152-6. (1996).

2.Lowes, R. Patient-Centered Care for Better Patient Adherence. Family Practice Management. (1998) http://www.aafp.org/fpm/980300fm/patient.html visited on 01 Jul 2010.

3.Slutsky, J.R. & Clancy, C.M. Patient-centered comparative effectiveness research: essential for high-quality care. Arch Intern Med. 170(5), 403-4. (2010).

4.Stone, A.A., Shiffman, S., Schwartz, J.E., Broderick, J.E. & Hufford, M.R. Patient non-compliance with paper diaries. BMJ. 324(7347), 1193-4. (2002).

5.Gwaltney, C.J., Shields, A.L. & Shiffman, S. Equivalence of electronic & paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value in Health. 11(2), 322-323. (2008).

6.Lamberti, M., Editor. State of the Clinical Trials Industry: A Sourcebook of Charts and Statistics, CenterWatch Publishing, 124-125, (2009).

7.Chang, C.H. Patient-reported outcomes measurement and management with innovative methodologies and technologies. Quality of Life Research. 16(1), 157-166. (2007).

8.U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research & Center for Devices and Radiological Health. Guidance for industry patient-reported outcomes measures: use in medical product development to support labeling claims. (2009).

9.Ross, J., Marcovitz, M. & Peck, R. Uncovering Reasons of Non-compliance in EPRO Studies to Improve PRO Data Collection. Presented at ISPOR 15th Annual International Meeting Atlanta, GA, USA May, 2010. http://www.ispor.org/research_study_digest/research_index.asp (2010).

10.Ross, J. & Marcovitz, M. Electronic PRO versus Paper PRO: What do the Patients Think? Presented at ISPOR 15th Annual International Meeting Atlanta, GA, USA. May, 2010. http://www.ispor.org/research_study_digest/research_index.asp (2010).

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Logistical Considerations in Central Laboratory Selection

PEER REVIEWED

Centralised Regional Laboratory Services for Clinical Trials

The rapid expansion of today's clinical trials into the world's emerging markets has exposed a number of logistical complexities. Seeking reduced drug development cycle time and costs, sponsors today search for eligible study participants in increasingly remote and heretofore underutilised geographies. At the same time, sponsors demand more complex laboratory testing, including a vast array of safety, predictive and efficacy biomarkers. In this shifting landscape, the "traditional" model of building "bricks and mortar" clinical trials-dedicated laboratories has become increasingly expensive and burdensome to both the central laboratory services providers and sponsors alike. In response, the industry is evolving to provide more cost-effective operating and logistical models to accommodate the complexity of today's clinical trials.

A Brief History of Central Laboratories

In the early 1980s nearly all laboratory work was conducted utilising "local" laboratories. Laboratory testing was primarily focused on safety rather than treatment efficacy. Benefits of this approach included low logistical expenditures, rapid result turnaround time, and little loss of sample integrity due to time and temperature exposure.

The 1990s witnessed a decided shift from "local" laboratories to large "central" laboratory facilities, able to quickly and efficiently process high volumes of samples. After a substantial up-front investment in facilities, information systems and laboratory personnel, central laboratory services providers enjoyed significant profit margins attributable to the low variable costs of processing safety samples. Furthermore, these large facilities were not only able to standardise the collection kits, but also consolidate the laboratory results into a single database, which improved consistency while reducing administrative costs. These advantages came at the expense of steadily increasing logistical costs and deteriorating sample integrity. Consequently, test cancellations increased as a result of time and temperature variables.

By the turn of the century, globalisation, mounting analytical complexity, and the inclusion of new treatment efficacy parameters apart from safety, posed heightened challenges for central laboratory services providers. Low sample volumes in non-traditional geographies coupled with high fixed costs forced service providers to choose among three undesirable realities: suffer reduced profitability; significantly increase test prices, or pass along high logistical costs of transporting samples long distances to the nearest "centralised" testing hub.

In today's clinical trial space, conducting studies in the more remote areas of the world is now a permanent fixture of pharmaceutical development. Large multinational trials often involve more than twenty countries, and four or more regulatory bodies, depending upon the registration strategy established by the sponsor. For reasons related to cost and geographic coverage, sponsors typically secure central laboratory services from virtual networks comprised of reference and clinical laboratories spanning multiple continents and regulatory agencies.

The current generation of central laboratory service providers seeks to combine the benefits of the "local" and "central" laboratory operating models. These providers leverage local labs for testing proximal to investigator sites. Working with local labs offers both capital and knowledge advantages. Capital benefits include access to existing facilities, information systems and test menus. Knowledge benefits are in the form of experienced laboratory personnel attuned to cultural, linguistic, and regulatory nuances. Simultaneously, these providers offer "traditional" central laboratory benefits including consistency, cost-efficacy and reliability through standardisation. Enabling standardisation are information systems, reporting platforms and harmonised operational processes.

Drug Safety Drives the Growth in Central Laboratory Services

Central laboratory data have represented more than 60% of all data submitted in an NDA for more than fifteen years. This percentage is expected to approach 80% within the next several years. The key driver behind a growing reliance on central laboratory data has been FDA guidance related to subject safety, and the subsequent reliance by industry on drug safety monitoring committees and post-marketing pharmacovigilance programmes. In order to maximise the ability of these efforts to detect drug-related effects, it is incumbent upon central laboratory service providers to develop and use globally harmonised analytical and data management platforms when delivering safety and screening parameters for subjects enrolled in clinical trials.

Market demand for central laboratory services has grown dramatically during the past decade, especially in the more remote and underdeveloped areas of the world, where large populations of drug-naïve patients are available for recruitment into new studies. Barclays Capital estimates the global market for central laboratory services to be approximately $2.3 billion.

In addition to the use of harmonised analytical platforms and global reference ranges, another factor positively influencing the growth of the central laboratory industry is value-added services. These include sophisticated data management capabilities, project services, study-specific clinical trial materials, logistics services, and specimen management.

Central Laboratory Services for Clinical Trials

Central laboratory services for clinical trials are complex, especially due to logistics associated with multinational studies. The central laboratories play an independent role in ensuring sample drawing kits and ancillaries (tubes and packing materials) are delivered in a timely fashion before the initiation of a study. To a central laboratory, "logistics" means "all activities to enable the timely arrival of a subject specimen and reporting the results back to the investigators." The graphic below shows the spectrum of functions of a full service central laboratory provider:

Manufacturer	Product	Analytical Application	Extended Lot No. Duration
Streck Omaha, NE , USA	Cal-Chex & Cal-Chex Plus	Haematology	90 days
Thermo Scientific MAS Waltham, MA, USA	chemTRAK H	Chemistry	18 months

Table 1: Major manufacturers of stabilised human-based control materials suitable for use in an interlab harmonisation programme.

A New Approach: Centralised Regional Laboratory Services Providers

Evolving as a reaction to today's clinical trial environment, some central laboratory service providers have successfully created global networks and offer centralised regional laboratory services to clinical trial sponsors. This new approach is applied in most cases globally (e.g. one facility in each continent); however, it may also serve as an effective solution on a regional scale (one facility within a distinct geo-cultural region (e.g. Eastern Europe)). For clinical trial sponsors, this approach provides significant advantages over the "traditional" central lab approach, including access to high volume laboratories with larger in-house test menus, reduced specimen transport costs, and enhanced knowledge of the local culture and applicable regulations. However, this model does not typically offer identical analytical platforms across all network laboratories. Central laboratories deploying this model must harmonise operations to ensure analytical rigour and regulatory compliance among these centralised regional laboratories.

Analytical Harmonisation

During the past 15 years, manufacturers of clinical laboratory instrumentation have significantly improved the technologies used to provide the safety and screening tests most commonly performed on clinical trials. Stricter adherence to calibrator assignments traceable to the WHO and other international consensus groups allows clinical laboratories operating disparate platforms to produce highly concordant laboratory data. Taken as a whole, these advances allow today's sponsors to secure services from networked laboratories that are cost-effective, and of similar quality to those produced by the largest players in this market.

Advances in instrument and reagent technologies notwithstanding, central laboratory service providers must nevertheless establish a rigorous harmonisation programme whose goal is to manage analytical bias among participating laboratories. Properly managed, an interlab harmonisation programme ensures the consistency and combinability of laboratory data provided

Features & Functionality	Description
HL7 Gateway Application	Ability to harmonise in real-time numeric and textual data received from disparate native LIMS environments
Data Harmonisation Engine	A middle-ware resident application that provides for real-time data mapping, qualification and validation into a single global database
Linchpin Data Architecture	Single-use accession numbers
Analytical Correction Factor Management	Application of correction factors derived from interlab harmonisation programme
Units of Measure (UOM) Management	SI and US conventional unit compatibility
Research Grade Data Analysis	For ad hoc analysis of study-specific data
Data Integrity	Suite of functionalities and background processes to ensure cleanliness of study-specific regulated data steam
Data Import Interface	Ability to set up and validate data importation routines from all levels and types of laboratory partners
Data Export	Ability to extract and export client-specific data transfer files in a variety of formats including CDISC and SAS
21 CFR Part 11 Compliance	Full validation at initial installation and ongoing validation thereafter with valid change control process
CDISC	Resident expertise in the CDISC protocol and data formatting and transfer functionality
Network Certification Agreement	An operational agreement executed among all network partners that describes interlab harmonisation efforts, process standardisation and the conduct of on-site quality audits and the funding of such efforts by the global organisation
Global Document Taxonomy	An agreed process and structure by which Standard Operating Procedures (SOPs), Working Practices Document (WPDs) and Standardised Forms (STFs) are authored and numbered by network service providers worldwide
Total Quality Management	The commitment by network partners to participate in a quality management programme, the description of the key elements to the programme, and the sharing of this commitment to sponsoring organisations.
Accreditations & Certifications	The agreement to secure and maintain regional and international accreditations and licenses relevant to sponsors conducting clinical trials in the international arena, including ISO EN 17025, ISO EN 15189 and CAP

Table 2: Key Functionalities for a central laboratory LIMS application intended for support of clinical trials in the international arena.

by network partners to their clinical trial clients. Improvements in the formulation and distribution of stabilised quality control materials have made this process both practical and manageable. The largest globally-situated manufacturers are able to sequester single lot numbers of materials and drop-ship specified quantities to networked laboratories on a pre-determined schedule. Moreover, unlike the situation 15 years ago, today's materials are derived from pooled human specimens and thus are free of the matrix-effects that confounded efforts to assess interlab bias across platforms and reagent methodologies. When undertaken in a rigorous and statistically valid manner, a well-designed interlab harmonisation programme can readily document analytical bias and utilise inter-node correction factors derived from a common reference point. Table 1 above lists commercially available quality control materials that the authors have successfully used to monitor analytical performance across a global network of twelve clinical laboratories

The ongoing analysis of quality control results across a network of laboratories is a significant part of an interlab harmonisation programme, and the major manufacturers offer software applications for use in managing QC results across an entire network of clinical labs. Based on a reflexive decision tree that must be established in advance of sample distribution, participating laboratories can readily resolve analytical bias and establish statistically valid correction factors.

Other Key Areas of Harmonisation

Central Laboratory Information Management System (CLIMS)

Another important element in successful interlab harmonisation is the selection of a central laboratory information management system (CLIMS) to acquire and manage laboratory data from each node in the network of service providers. Toward that end, one of the most important technological advances that has allowed the development of virtual global laboratory networks is the HL-7 data transmission standard that is used within the global healthcare system. An list of the functionalities that are essential for supporting the laboratory aspects of international clinical trials are listed in Table 2.

Conclusions

Central laboratory services providers continue to evolve in response to the changing landscape of clinical trials. In the 1980s and 1990s, the industry evolved from strictly "local" laboratories to "central" laboratories. The new generation of central laboratory

providers seek to accommodate the increasing geographic and analytical complexity of today's clinical trials by deploying harmonisation strategies across centralised regional laboratories, offering the benefits of both "local" and "central" frameworks. This new model enables sponsors to cost-effectively enjoy access to geographically remote regions, while at the same time reaping the benefits of centralised reporting, analytical rigour and regulatory compliance.

References:
1. Stephen DeSantis, "Rising Stars in the Central Lab Market," CenterWatch Monthly, Vol 13, Issue 5, May 2006

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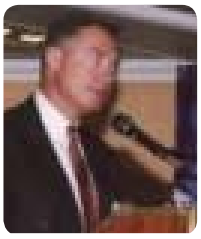
Eric Hayashi is president and CEO of LabConnect, LLC, a global provider of centralised laboratory testing services for the biopharmaceutical industry, and is an eighteen-year veteran of the clinical trials industry. He holds an MBA from the Wharton School of the University of Pennsylvania and a BA from Whitman College, and is an affiliate professor at the University of Washington's masters' degree programme in clinical trials. Prior to LabConnect he was Vice President, Corporate Development for Radiant Research, where he continuously served on the company's three-person executive team, and was responsible for sales, marketing and acquisition activities, and was instrumental in its growth to 1000 employees over six years. Eric and his family reside in Seattle, Wash.



Frank Morrow, PhD, FACN is chief operating officer of LabConnect, LLC. Dr Morrow is a veteran of the central lab business, having served as Founder, President and Chief Scientific Officer at Quintiles Laboratories Worldwide, where he was responsible for the division's growth from inception to more than $110M in revenue, 1000 employees, and five wholly-owned central laboratory facilities worldwide over ten years. Subsequent to Quintiles, he served as VP, Worldwide Operations / VP, Systems Integration & Strategic Planning at Quest Diagnostics Clinical Trials. Dr Morrow has his clinical laboratory directorship license in more than ten states, a PhD in Clinical Biochemistry (University of Georgia) and his MS in Human Physiology (Penn State). Prior to his business career, he taught for six years at Tufts and served as Director of the Nutrition Evaluation Laboratory of the USDA Human Nutrition Research Center on Aging, where he helped establish the nation's RDAs for vitamins B12, B1 and B6.

DIA 46th Annual Meeting (2010) – Washington DC. *A Review*

The five-day 46th DIA 2010 Annual Meeting started on June 13. It was a great success and Washington, DC was an excellent location. In addition to the thousands of industry attendees, there were over 400 exhibiting companies. On Monday, the keynote speaker, Margaret A. Hamburg, MD, Commissioner of the US Food and Drug Administration, started proceedings with a focus on regulatory science and the need for strengthening of FDA controls with regards to the globalisation of medical products. The heparin recall and melamine recall highlighted the urgency of partnering with regulatory bodies in other countries. Throughout the various meetings the important topics were comparative effectiveness and regulatory controls with respect to who makes the regulatory decisions (the FDA? A pharmaceutical firm? A consumer decision?) How is this done in the EU or the US?

Dr Huang from the FDA, Dr Narayanan from the MHRA, Dr Ladenheim from AtherSys and Dr Watkins from Aastrom Biosciences, as well as media representatives from the Journal for Clinical Studies, were present at a meeting entitled "From Bench to Bedside: Challenges in Bringing Novel Cell-based Therapies from Experimental Studies into Successful Clinical Programs", where some industry challenging issues were discussed. At a session on Modelling and Simulation, the FDA encouraged sponsors to perform modelling early in clinical development. At another session, on biomarkers, sponsors indicated that they are now looking at biomarkers to help their decision-making on go/no-go points during early clinical development.

In terms of the core topic for JCS, the session on "Clinical Trials in the Fast Lane: Is There a Speed Limit on the Road to Excellence?" was of particular relevance. The main points were: (1) increasing the speed of clinical trials means avoiding speed bumps. These speed bumps are delays in study start-up, delays on enrolment, and delays in resolving data queries; (2) to avoid these speed bumps, various sponsors and CROs are using metrics as indicators of the speed and quality of the conduct of a clinical trial; however, the metric must be carefully chosen; (3) the metrics must be available on a day-to-day basis for the clinical trial manager and the clinical research associate. This would allow any necessary corrective action to be taken early, and make for a more efficiently-run trial; (4) these metrics should be simple and visually displayed.

A major theme at DIA was patient recruitment and retention, by way of educational sessions and at the main floor show. The conference featured more than a dozen panels exploring the related topics. Mr Kremidas, VP, global head of patient recruitment at Quintiles, who was involved in several sessions on patient recruitment, explored areas such as who is accountable for clinical trial enrolment and the importance of using centralised outreach tools at the site level. On patient recruitment, BBK Worldwide introduced its Patient Recruitment Franchise Program. BBK's flagship product for its new program is the FRANCHISE e-BINDERSM, a flexible and intuitive communication platform that uses the Apple iPad® to facilitate the myriad processes necessary to effectively recruit and manage patients for global clinical trials. This new franchise model not only realises significant cost savings in the execution of patient recruitment programmes, it also supports quick, efficient enrolment for multiple studies within the same therapeutic category, as well as multiple protocols for a single compound. "Franchise programmes create exponential savings through the economies of scale derived from applying strategies and tactics across multiple studies and countries," said Joan F. Bachenheimer, BBK Worldwide founding principal and CEO. "Using the model of the Patient Recruitment Franchise Program, sponsors are able to consolidate planning and recruitment strategies for immediate and long-term cost reductions that far exceed preferred pricing or volume discounts."

JCS looks forward to meeting our existing and newly networked colleagues at the 47th DIA Annual Meeting, 26th-30th June 2011, in Chicago, USA.

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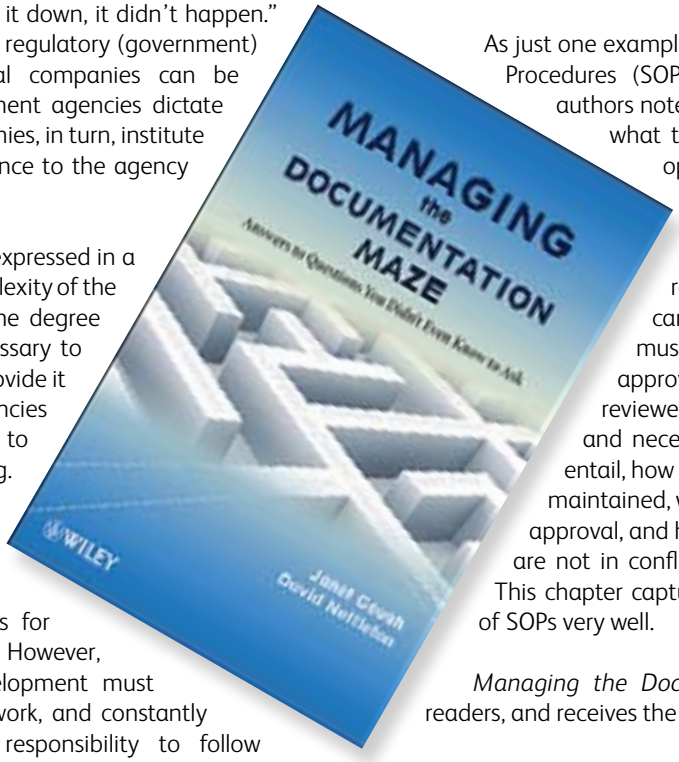
Managing the Documentation Maze:
Answers to Questions You Didn't Even Know to Ask by Janet Gough and David Nettleton

Many industries operate under strict regulation, and the healthcare industry is no exception. The regulatory process requires an enormous amount of documentation, which must be complete, accurate, and available (retrievable from its storage medium) in a reasonable time. As noted by the authors of *Managing the Document Maze*, the position of regulatory agencies across the globe is clear: "If you didn't write it down, it didn't happen." The two-way interaction between regulatory (government) agencies and biopharmaceutical companies can be represented as follows: "Government agencies dictate what companies must do. Companies, in turn, institute good practices that show adherence to the agency requirements."



While these principles can be expressed in a straightforward manner, the complexity of the necessary documentation, and the degree of organisation and control necessary to create it, maintain it, retrieve it, provide it to inspectors from regulatory agencies when required, and submit it to regulatory agencies, is staggering. Many document management professionals within companies are dedicated to such tasks, and need to be intimately familiar with the respective requirements for document creation and control. However, everyone involved in drug development must be aware of the need for such work, and constantly vigilant with regard to their responsibility to follow instructional documents, and to maintain comprehensive and accurate records of their activities.

Managing the Document Maze takes a fascinating and extremely effective approach to its topic. Chapters start with brief scene-setting introductions, that are followed by extensive sets of questions related to the chapter's focus. Pragmatic answers are then provided in turn. This organisational framework makes it very easy to target information that will answer specific questions of interest to the reader, while also providing a comprehensive overview of key information. Topics covered include: principles of document management; Part 11 compliance; Standard Operating Procedures; non-clinical records; clinical and submission records; consistency and readability in documents; and maintaining inspection readiness. There is also a sizeable Appendix covering the Federal Register.

As just one example, Chapter 7 on Standard Operating Procedures (SOPs) is extremely readable. As the authors note, SOPs "show how companies apply what the regulations say to their specific operations. As such, they must be clear, they must be true, and they must work together." The importance of writing, maintaining, revising, and implementing SOPs cannot be overstated. Attention must be paid to how they are to be approved, how existing SOPs are to be reviewed to ensure they are still current and necessary, what the review process will entail, how appropriate cross-referencing will be maintained, who has ultimate signatory power of approval, and how to ensure that site-specific SOPs are not in conflict with company-wide documents. This chapter captures the spirit and the practicalities of SOPs very well.

Managing the Document Maze is recommended to readers, and receives the JCS Library Award.

Reviewed by J. Rick Turner

Please note: Like the reviewer, Dr. Huml is an employee of Quintiles.

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J. Rick Turner, PhD, Editor-in-Chief, joined the journal's Editorial Board this January. He is Senior Scientific Director, Cardiac Safety Services at Quintiles, and also an accomplished author and editor who has a real passion for books. We are pleased to announce that Rick has agreed to become Editor-in-Chief of a new addition to our journal, the JCS Book Corner. He will be reviewing books of interest to our readership, and giving JCS Library Awards to outstanding books that should be in your company's library, or perhaps even in your personal collection. On occasion, he will be inviting other Editors to review books too.

Rick's first book was written while he was actively involved in research in the field of Cardiovascular Behavioral Medicine. Entitled Cardiovascular Reactivity and Stress: Patterns of Physiological Response (1994, New York: Plenum Press) it was the first student textbook examining the putative role of psychological and behavioral stress in the development of high blood pressure, and potentially other cardiovascular sequelae. The journal Psychophysiology commented that "Cardiovascular Reactivity and Stress is an extremely readable and well organized text… As an introduction to the field, Turner's book is a superb resource." Rick edited four other books in the field of Behavioral Medicine before moving into the pharmaceutical industry in 1996.

Since being in this industry, Rick has published three books discussing various issues within new drug development. The first, New Drug Development (2007, Hoboken, NJ: John Wiley & Sons) was a general overview of this topic. The Journal of Applied Statistics commented that "The book gives a refreshing run through of the drug discovery and development process and it is probably the book you need to have to learn about this fascinating field." An updated, expanded, and less technical second edition will be published later this year by Springer Science (New York). His other books, both co-authored with Todd Durham, are Introduction to Statistics in Pharmaceutical Trials (2008, London: Pharmaceutical Press) and Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance (2009, Hoboken, NJ: John Wiley & Sons).

We are delighted that Rick is bringing his publishing experience and his love of books to the journal, and we particularly look forward to featuring books written by our readers. If you would like to submit your book to the JCS Book Corner for review, please ask your publisher to send a copy to: **Pharma Publications, Building K Unit 104, Tower Bridge Business Complex, Tower Point, London, SE16 4DG**

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News

Biotec invest in ultra low temperature storage

Leading UK-based pharmaceutical services company, Biotec Services International, has expanded its ultra low temperature storage capacity to accommodate growing demand for the long term storage of biopharmaceuticals.
The increase in ultra low temperature storage space by 300 % will enable Biotec Services International to meet the needs of its contract manufacturers who use its import, QP certification, labelling, assembly storage and worldwide distribution services for materials in active clinical trials.
The move comes as the company looks to expand its offerings to meet the needs of a number of blue chip international pharmaceutical and healthcare clients.

Source: Fresh Baked PR.

Medidata release two significant products

Medidata Balance™
A new randomization and trial management solution (RTSM) that offers sponsors and sites a simplified but sophisticated tool for randomizing subjects and managing clinical supply usage for study designers, biostatisticians, trial managers and investigator sites – replacing interactive voice response (IVR) and interactive web response (IWR) systems.

Medidata Grants Manager 3.0™
Now part of PICAS®, Medidata's unique database of negotiated trial costs, Grants Manager 3.0's new complexity metrics measure the actual difficulty and work required of sites in conducting clinical trials, reducing cost, time and risk.

Source: Louis Paul Partners

Saudi Food and Drug Authority Suspends The Authorisation of Rosiglitazone (AvandiaÂ)

The Saudi food and Drug Authority has reviewed the safety of Rosiglitazone (AvandiaÂ®) which used in treatment of type 2 diabetes mellitus and marketed in Saudi Arabia as AvandiaÂ®. Based on growing evidence from clinical trials meta-analyses and observational studies indicating serious cardiovascular adverse events associated with the use of rosiglitazone as, the Advisory Committee for Pharmacovigilance in Saudi Arabia has concluded the followings:
1. The risk of using rosiglitazone outweighs its benefit especially risks of cardiovascular events including myocardial infarction and congestive heart failure in addition to increased risk of fractures.
2. Safer alternatives could be used for treatment of diabetes mellitus are available in Saudi Arabia.
Based on the review it was recommended to suspended rosiglitazone containing product.

For further information, please visit: http://www.sfda.gov.sa

Pneumococcal Vaccine Offers Protection to HIV-Infected African Adults in Clinical Trial

A clinical trial of a vaccine against a major cause of pneumonia and meningitis has shown that it can prevent three out of four cases of re-infection in HIV-infected adults in Africa.

The trials, conducted in Malawi and funded by the Wellcome Trust, studied the efficacy of a vaccine against infection with the Streptococcus pneumoniae bacteria. These bacteria are a primary cause of pneumonia and when they invade the blood stream and brain -- so called invasive pneumococcal disease (IPD) -- they cause the serious and often fatal illnesses of septicaemia and meningitis. In HIV-infected adults, particularly in sub-Saharan Africa, the risk of developing IPD increases between thirty and a hundred-fold.

Researchers at the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine in Blantyre, Malawi, tested the efficacy of Prevnar, a pneumococcal conjugate vaccine (PCV) developed by pharmaceutical company Wyeth, in a double-blind randomized placebo-controlled clinical efficacy trial. The results are published in the New England Journal of Medicine.

The trial, led by Dr Neil French, formerly at the Liverpool school of Tropical Medicine, tested the vaccine on almost five hundred predominantly HIV-infected adults who recovered from IPD after being admitted to the Queen Elizabeth Central Hospital in Blantyre. They found that the vaccine prevented 74% of recurrent cases of IPD in patients with underlying HIV infection.

Source: Science Daily

New Regulations to Boost Indian Clinical Trials Industry

With new government incentives and policies coming into pipeline, the Indian clinical trials market is expected to grow at a CAGR of around 31% during FY 2010 – FY 2012

According to our new research report "Booming Clinical Trials Market in India", India is anticipated to become one of the most lucrative destinations for clinical research outsourcing in coming years. The future outlook of the Indian clinical trials market remains buoyant as it will grow at a CAGR of around 31% during the forecast period FY 2010-FY 2012. Various factor like new government incentives & policies will spur growth in the industry.

Research indicates the clinical trials market will help many allied sectors like IVD industry and educational industry to accelerate their growth pace. In addition, the market will observe opening up of many job opportunities for young professionals in the coming years.

"Booming Clinical Trials Market in India" provides detailed information about the cost associated with different clinical trials phase. It also elaborates on the contribution of government regulation in the growth of clinical trials industry in the country. Apart from this extensive research on success and risk factors for clinical trials industry has been done. Further, the report covers an in-depth analysis of various industry parameters like global clinical market trends, size and patient pool availability, infrastructure and expertise.

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