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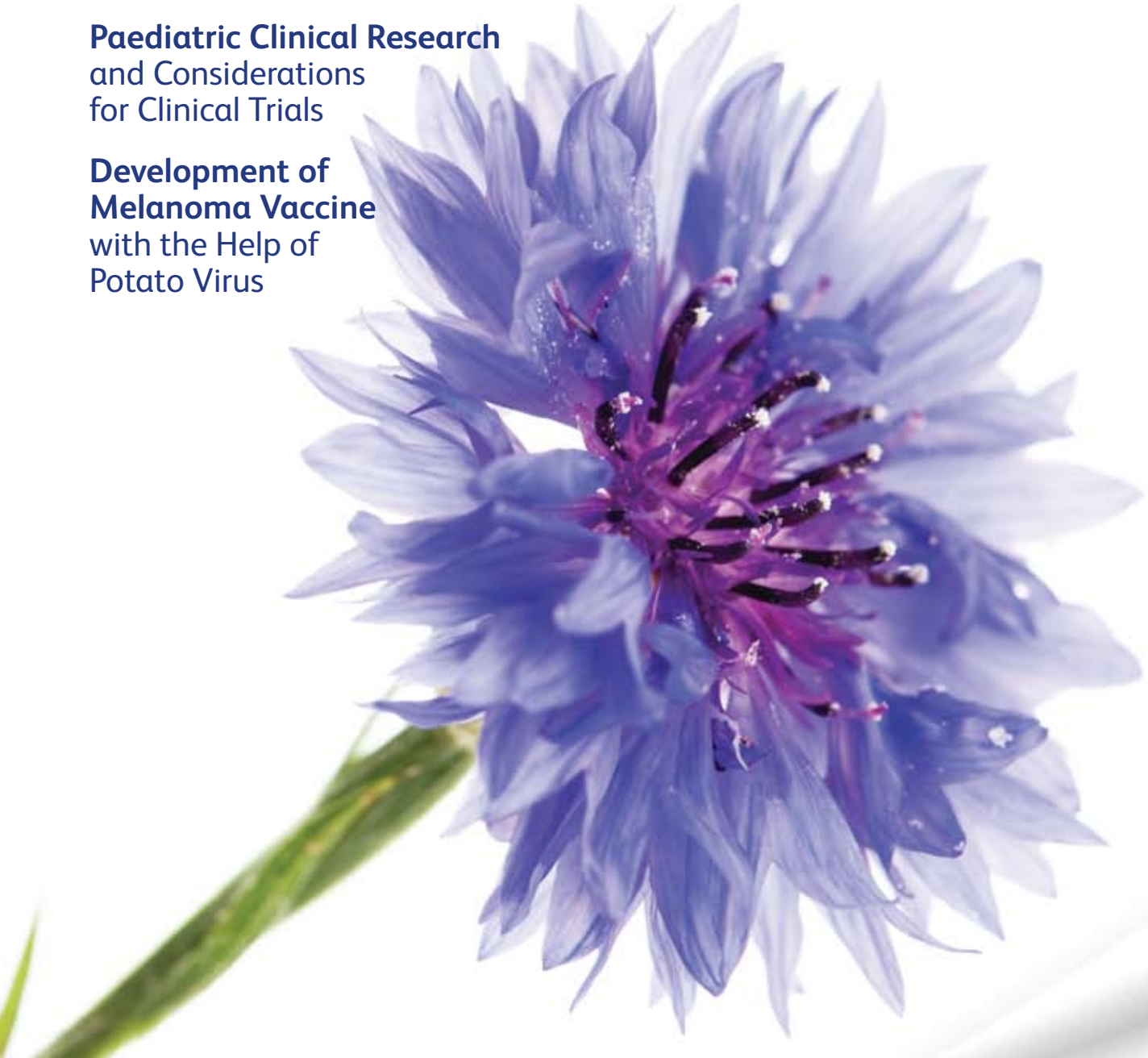

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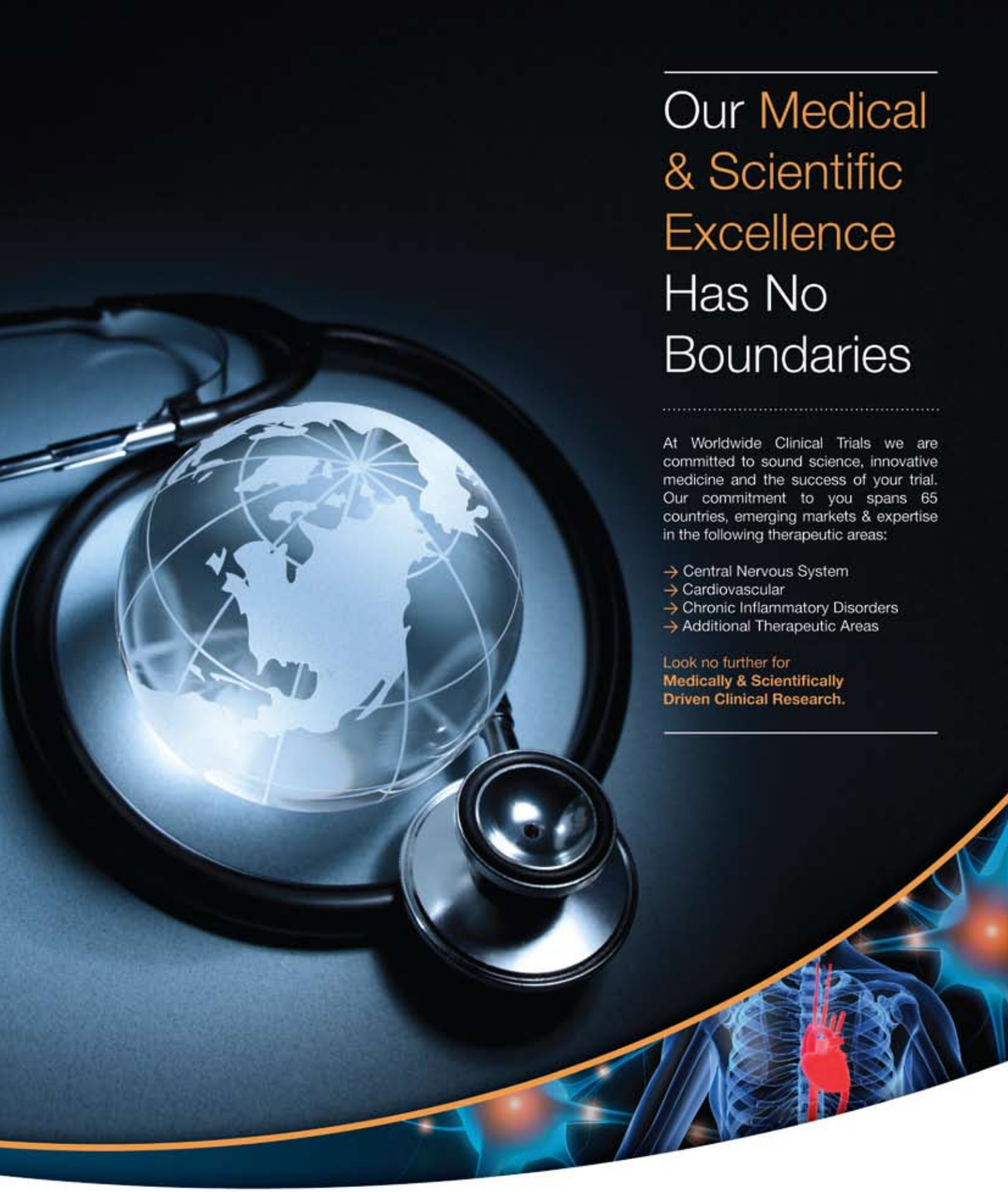

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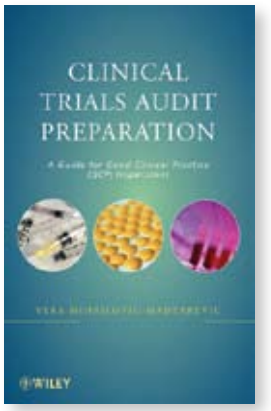

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Welcome to the latest edition of our Journal. Once again the issue is packed with a diverse range of interesting articles covering a broad spectrum of topics. Looking through the array of topics, some themes emerge that illustrate the nature of the sector we all work in. The first thing that struck me, as if I needed any reminding, is the truly global nature of our business. Clinical work is being carried out pretty much everywhere, and each location has something different to offer, as well as presenting its own blend of challenges. This month we have articles covering specific locations such as South Africa, Latin America and India, and we bring you a feature from Estonia by Riin Ehin on work being done on developing cancer vaccines from potato virus.

The second theme that is prominent is the impact of regulation on the clinical workflow, especially with regard to research, the management of trials and the launch of product to market. From J Rick Turner's piece about the impact of the FDA advisory notices on cardiovascular safety (this issue he explains how the FDA uses REMS as a tool to mitigate overall risk) through to Walter Chalkley's piece on the FDA's proposed rule governing the reporting of information regarding falsification of data, there is plenty of advice and guidance on how to cope with the rigours imposed by the increasingly complex regulatory environment.

Complexity is a recurring them too. Nothing seems simple these days. In the September 2010 issue, we brought you a detailed view of etiopathogenesis in relation to respiratory diseases in children, and explained the complexities presented when regulation and directives have slightly different purposes. In this case an EU paediatric regulation and a directive on clinical trials have produced inconsistencies between member states in the requirements for running some trials, making the decision-making process for conducting trials more complex, and therefore more difficult. In this November issue, we continue with the very important topic of paediatrics, where Rick Turner and Cynthia Jackson explain the factors affecting paediatric clinical trials and their regulations.

In another piece, Dr Alvin gives an insight into where we should focus in terms of reproductive therapeutic solutions in her look at testosterone replacement therapy in Adult Testosterone Deficiency Syndrome. She suggests future clinical trials should also examine treatment patterns among men with symptomatic androgen deficiency, and the profile of asymptomatic men with low testosterone levels, which might assist in understanding the mechanisms by which low testosterone levels increase risk of disease.

We have incorporated a new CNS Watch page starting from this issue. Henry J. Riordan starts with DSM-5's impact on psychiatric clinical trials. In recent years, the DSM-5 Task Force and Work Group members have been labouring to revise DSM-IV-TR criteria to reflect recent advances in the science and conceptualisation of mental disorders. I hope you find this valuable.

This issue also has a wealth of advice aimed at speeding processes up, dealing effectively with necessary regulation and ultimately improving efficiency, and therefore the returns to be made on the considerable investment required in today's clinical world. Benjamin Jackson concentrates on the importance of relationships to the success of the recruitment of patients for trials conducted in global trials; and Joseph Bedford explains the value of interactive voice and web response systems in global clinical trials.

It seems that many of us need some help to find clarity and understanding in the maelstrom that we know as modern business life, and indeed life in general. A few quiet minutes spent reading and considering this month's content may well go a long way towards making this particular corner of our daily existence a little easier to deal with. On a closing note to 2010, we would like to wish all of you a Very Merry Christmas and a Prosperous New Year.

Andrew King, Managing Director, Biocair International

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FDA's Proposed Rule: Reporting Information Regarding Falsification of Data

In early 2010, the US Food and Drug Administration (FDA) proposed adding to its reporting regulations a requirement that sponsors of regulated products submitted to the Agency must report any real or suspected falsified data related to "reporting study results, or in the course of proposing, designing, performing, recording, supervising, or reviewing studies that involve human subjects or animal subjects conducted by or on behalf of a sponsor."[1] This proposed rule would give sponsors 45 calendar days following discovery to report the falsification. Through this reporting system, the FDA hopes to improve the integrity of the data used to approve products, as well as protect the safety and wellbeing of clinical trial subjects.

The new rule would be amended to regulations in 10 areas related to clinical and nonclinical studies of human and animal food, drug, and dietary supplements, including 21 Code of Federal Regulations (CFR) Part 312 (investigational new drug applications) and 21 CFR Part 58 (good laboratory practice for nonclinical laboratory studies). Despite the research misconduct mandates found in the Public Health Services (PHS) regulations at 42 CFR Part 93 and the National Science Foundation (NSF) regulations at 45 CFR Part 689, the FDA believes those regulations focused on narrow criteria regarding which research was covered by those requirements. With this new regulation, the Agency seeks to cover all types of studies subject to FDA evaluation.

Specifically, falsification is defined as "creating, altering, recording, or omitting data in such a way that the data do not represent what actually occurred" and would undermine the studies' reliability. The Agency notes cases in which sponsors excluded data from a clinician suspected of falsifying data, and dismissed the clinician, but did not inform the FDA. Similar cases occurred where the clinician was reprimanded internally but retained without notification to the FDA. These instances are a concern, since these investigators may continue to conduct and participate in the design and execution of future studies.

The FDA notes the proposed rule does not mandate the reporting of errors such as transposed numbers or misspellings. However, the rule does mention that separating errors from falsifications may be difficult, as perpetrators may attempt to cite the suspect data as an "error" if discovered. The FDA suggests investigating past studies that involved the clinician to verify if other such "errors" have been noted, since such behaviour is often repeated over multiple studies. Public comments submitted to the FDA from clinical organisations encourage a more specific definition of the term "errors" and its separation from "suspected falsification", since the former (not reportable) could be investigated as the latter (reportable).[2]

The FDA has stated that 45 calendar days is sufficient time for a sponsor to investigate any suspected falsification and report the incident. Failure to report in this timeframe could potentially be a violation of section 301 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Public comments from developer stakeholders have suggested that the timeframe should be broadened as a thorough investigation would likely take longer.[3]

References

1. *Federal Register: February 19, 2010. Volume 75, Number 33, 7412-7426.*
2. *Regulations.gov: Docket FDA–2008–N–0115 Summary [Internet]. Washington. Reporting Information Regarding Falsification of Data; 2010 June 28 [2010 September 15]. Available from: http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2008-N-0115*
3. *Ibid.*

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Cardiovascular Safety Watch Column

The September issue of this column discussed a meeting of two US Food and Drug Administration (FDA) Advisory Committees in July 2010 that examined evidence pertaining to the cardiovascular safety of rosiglitazone.[1] The members' votes were known at the time of writing that column, and hence discussed in it, but at that point the FDA had not made any public statement on whether it would follow the committees' recommendations (advisory committees' recommendations are not binding). Since then, the FDA has done so, and this column therefore provides an update.

In concordance with the overall recommendation of the advisory committees' members, the FDA did not withdraw rosiglitazone from the US market, but it took several actions, including a requirement for the drug's sponsor to submit a Risk Evaluation and Mitigation Strategy (REMS) within 60 days of the FDA's announcement on September 23rd 2010. The REMS is a tool available to the FDA to mitigate overall risk, making the drug available to certain patients under circumstances that make the treatment benefit-risk profile acceptable, while not allowing its use in other patients for whom the benefit-risk profile is likely to be unfavourable.

The REMS approach was introduced in the Food and Drug Administration Amendments Act of 2007 (FDAAA), which became effective on 1st October 2007.[2] Title IX, 'Enhanced Authorities regarding Postmarket Safety of Drugs,' provided the FDA with increased funding and sweeping new authorities in the safety domain. Section 901, Subtitle A, 'Postmarket Studies and Surveillance,' introduced the REMS. Prior to approving a drug for marketing, the FDA can require a sponsor to provide a REMS that addresses how risk will be mitigated (hence safety optimised) once the drug is marketed. Additionally, if the FDA becomes aware of 'new safety information' concerning a drug that is already marketed - new safety information being defined as information tied to a (perceived) serious risk associated with the drug – the agency can require a REMS to be submitted at that stage in the drug's lifecycle. This author has discussed the individual elements that can be included in a REMS previously.[3]

The required elements in the REMS for rosiglitazone include:[4]

- Provision of complete risk information to each patient, and documentation in his/her medical record that this information has been received and understood;
- Documentation from healthcare providers that each patient taking rosiglitazone falls into one of two groups:

1. Patients currently taking rosiglitazone;
2. Other individuals who are not able to achieve glycemic control on other medications, and who decide in consultation with their healthcare professional not to take pioglitazone (the other thiazolidinedione on the market) for medical reasons.

- Documentation from healthcare providers that the risk information has been shared with each patient;
- Physician, patient, and pharmacist enrolment.

While this restricted access is likely to reduce the number of individuals who will take the drug, rosiglitazone will stay on the US market and hence be available to patients for whom alternative treatment options are considered by them and their physicians to be less suitable.

Regulatory activity concerning rosiglitazone has also recently occurred in the European Union. As announced on the same day as the FDA's decision, the EMA's Committee for Medicinal Products for Human Use (CHMP) voted to remove the drug from the European markets: the European Commission will make the final decision that will be legally binding for the 27 member countries in the European Union. The CHMP recommended the suspension of marketing authorisations for rosiglitazone and combination medications containing the drug (rosiglitazone/glimepiride and rosiglitazone/metformin). As noted on the EMA's website, "These medicines will stop being available in Europe within the next few months. Patients who are currently taking these medicines should make an appointment with their doctor to discuss suitable alternative treatments. Patients are advised not to stop their medication without speaking to their doctor."[5]

The difference in regulatory viewpoints is not the result of widely diverging assessments of the available data: rather, it reflects "the power of REMS."[4] While the REMS can be viewed in a negative light, it can also be viewed very positively. The case of rosiglitazone provides such an example: a REMS is being used to facilitate the continued availability and use of the drug by a select group of patients for whom its benefit-risk balance is favourable. The EMA has no equivalent tool at its disposal, and hence marketing withdrawal is its recommended action, meaning that the drug is no longer available for any patient.

References

1. *Turner JR, 2010, Cardiovascular Safety Watch column. Journal for Clinical Studies, September issue, 12.*
2. *110th US Congress. Food and Drug Administration Amendments Act; September 2007. http://frwebgate.access.gpo.gov/cgibin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110. (Accessed 15th October 2010)*
3. *Turner JR, 2009, Drug safety, medication safety, patient safety: An overview of recent FDA guidances and initiatives. Regulatory Rapporteur, 6(April issue):4-8.*
4. *Sutter S, Davis J, 2010, FDA, EMA decisions on Avandia reflect the power of REMS. "The Pink Sheet:" Prescription Pharmaceuticals and Biotechnology, September 27th, 1 and 4-6.*
5. *www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001122.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1 (Accessed 15th October 2010)*

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Translational Research Excellence and Promises

The 2010 Translational Research Excellence conference (TRX10) was held in Brisbane, Australia, 11-13 October, 2010. The conference's theme was "Collaborate to Innovate", with approximately 100 speakers from academic institutes and industry who addressed applied discoveries in a number of disease areas: stem cell-based therapies; genomic and proteomic biomarkers in, for example, cardiac and renal transplantation; preclinical and clinical research; next generation sequencing and systems biology; issues in developing, and scientific issues in registering, biologics and biosimilars; and supporting and commercialising translational research of therapeutics.

Examples of the speakers and topics covered included Prof. Yoichi Kurebayashi, Director, Translational Research Innovation Center, Kobe University, Japan, who illustrated the conference's theme with his presentation on the role and value of the academia-industry partnership as a powerful enabler of drug discovery translation that is thought to be a key to address the issue of Phase II attrition. A large part of the reason for the drug developmental attrition during Phase II is that companies have been increasingly targeting complex diseases with high unmet medical need, and these complex diseases involve novel mechanisms of action and/or unprecedented targets associated with higher attrition risk. Issues in target validation and lack of preclinical disease models warrant the engagement of scientists from different disciplines, and partnerships between academia and industry to close the gaps in drug discovery, for example between understanding of the disease pathology and target validation or in the preclinical area. Prof. Ric Day, Therapeutics Centre, University of New South Wales, Australia, and current president of the Drug Information Association (DIA), concurred with the need for smart academia-industry partnerships, and illustrated the challenges to be overcome.

Kaley Wilson, PhD, of the Centre for Drug Research and Development (CDRD) in Vancouver, Canada, explained how the CDRD tries to support academic investigators to translate their discoveries into new therapeutics by providing an infrastructure and staff to perform proof of concept studies in the preclinical environment. Tony Peacock, CEO of the Cooperative Research Centres (CRCs) in Australia, highlighted the roles of the medical CRCs in Australia, such as the ones for Biomarker Translation, Biomedical Imaging Development and Cancer Therapeutics.

Dr Chris Holloway of ERA Consulting, UK, presented many case studies showing that lack of awareness of potential regulatory concerns at an early stage of R&D can eventually lead to failure of the product at the stage of marketing authorisation, and ignoring indicators of problems with a product can, literally, be fatal – and therefore ongoing understanding of the biology of complex products is crucial. In the same spirit, Dr Chaline Brown of Ground Zero Pharmaceuticals, USA, explained that regulators see the generation of pharmacogenomic data as a top priority, and both EMA and FDA are open for "stakeholder" input on the process.

Prof. Mark Kendall, Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Australia, presented the Nanopatch™ which contains an array of densely packed projections invisible to the human eye, and capable of injecting vaccines at low doses that elicit excellent immune responses. Prof. Silviu Itescu, CEO of Mesoblast Ltd, based in Melbourne, Australia, provided an overview of the application of stem cell therapy involving mesenchymal precursor cells in heart disease.

Prof. Zee Upton, Tissue Repair and Regeneration Program, Institute of Health and Biomedical Innovation, Queensland University of Technology, Australia, described the pathway from discovery to clinical trials of topical administration of growth factors in wound healing. Promising results were obtained in two clinical trials examining the potential of novel complexes involving extracellular matrix (ECM) proteins such as vitronectin (VN) as a treatment for venous and diabetic ulcers.

Dr James Garner, Vice President and General Manager at Takeda Clinical Research, Singapore, Mr Russell Neal, COO of CNS Pty Ltd, Australia, and Mr Gerard Dunne, Managing Director of Beltas, New Zealand, reviewed the pros and cons of conducting clinical trials in Australia and New Zealand. While the researchers in Australia generate significant academic activity as measured by scientific publications and patent applications, the increase in experienced investigators in Asia poses new challenges. Since both countries feature fast clinical trial approval processes, capable and willing investigators and an amenable research environment, they should expand collaboration with the global research community to keep its preeminent place in drug development.

As one can see, the range of topics and calibre of speakers augurs well for the next Translation Research Excellence Conference (TRX12) planned for 23-26 October 2012, which will also be held in Brisbane, Australia.

Mario Pennisi Chief Executive Officer, Queensland Clinical Trials Network Inc. (QCTN) Mario has extensive experience managing laboratory medicine services. In the mid 1990s, in affiliation with US and German-based organisations, he established the first Queensland-based 'central laboratory' in order to service international trials in the Asia-Pacific region. He was also a founding member of Queensland's first contract research organisation.

Since establishing in 2005, Mario has overseen QCTN's growth to become Australia's peak industry group for therapeutic product service providers – now representing over 100 members with numerous strategic partners across the Asia Pacific Region and in Germany.

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DSM-5's Impact on Psychiatric Clinical Trials: Challenges and Opportunities

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is considered to be the standard for diagnostic criteria of psychiatric disorders, and the DSM-IV-Text Revision (TR) is extensively used by a broad range of international healthcare professionals in a wide variety of clinical and research settings. The DSM is also extensively utilised in a variety of psychiatric clinical trials, and is relied upon heavily by regulatory agencies for labelling purposes. In recent years, the DSM-5 Task Force and Work Group members have been labouring to revise DSM-IV-TR criteria to reflect recent advances in the science and conceptualisation of mental disorders. This brief review will summarise some of the more salient proposed criteria revisions, their implications for psychiatric trials, and resultant opportunities for psychiatric drug developers.

Although it is impossible to predict the exact criteria that will be part of the final DSM-5, it is important for psychiatry drug developers to closely monitor the progress of DSM-5, and to make adjustments that incorporate applicable revisions in their development programmes. There is some urgency to this task, as Phase 1 field trials are currently underway and members of the DSM-5 Task Force and Work Group have already disseminated initial text revisions of the DSM-5 for public review. In the spring of 2011, revisions to these proposed criteria (based on results from the first phase of field trials) will be tested again in a second phase of field trials, culminating in the publication of DSM-5 at APA's 2013 Annual Meeting in San Francisco[1]. Given the length of psychiatric drug development programmes, the implementation of DSM-5 will undoubtedly have near-term ramifications in terms of trial conduct (from diagnostic schemas to endpoints and scales), regulatory appraisal, and even the potential marketing of pharmaceutical products to physicians and patients.

DMS-5 draft criteria revisions have already been suggested for numerous drug treatment indications, including substance-related disorders, schizophrenia and other psychotic disorders, mood and anxiety disorders, eating and sleep disorders, and delirium, dementia, amnesia, and other cognitive disorders. Some of these changes will involve patients currently diagnosed with one disorder being classified elsewhere, while other changes may serve to provide only clarification. For example, in the revised criteria for schizophrenia, the former DSM-IV-TR subtypes of disorganised, paranoid, undifferentiated, and residual schizophrenia (which have been used extensively in both acute and chronic schizophrenia trials for inclusion purposes) may be abandoned in favour of various symptoms or "dimensions", such as hallucinations, delusions, disorganisation, restricted emotional expression, avolition, impaired cognition, depression, and mania.

Although there may be some difficulties in making comparisons to traditional DSM-IV-TR criteria, the use of "dimensions" may actually increase the validity of certain diagnostic criteria and provide a more multidimensional and holistic assessment of a patient's condition, including disease severity, functional level, and quality of life. Adding dimensions to diagnostic criteria will also necessitate the design and validation of novel and more complex outcome measures and improved patient-reported outcomes. This feature of DSM-5 should also result in better concordance between DSM and ICD, with improvement in comparability of data obtained from clinical trials in different regions of the world.

As another example, the concept of "catatonia" is likely to be removed from the new schizophrenia criteria, and may become a diagnostic class within psychosis, or a specifier to psychosis or mood disorders. Therefore, some schizophrenics will be reclassified. Reclassifying catatonia outside schizophrenia could potentially open the way for novel drugs, as the optimal treatment for catatonia is likely to differ from the standard treatment for schizophrenia. For example, dopamine D2 blockade (the current standard drug therapy for schizophrenia) may be contraindicated in a new drug treatment claim for catatonia.

The DSM-5 work group is considering adding a novel criteria related to "Psychosis Risk Syndrome", which is characterised by a progressive and distressing (but attenuated) form of delusions, hallucinations, and disorganised speech, despite intact reality testing. The concept of a risk syndrome that precedes the full-blown disorder has been well accepted in other disciplines, and in some CNS disorders such as Alzheimer's disease. Although controversial (primarily due to stigmatisation and the possibility of false positive diagnosis), if validated this syndrome may advance trials in high-risk individuals and form the basis for a new drug treatment claim. Recent studies of long-chain fatty acids have supported the value of treating at-risk patients by reducing progression to psychotic disorders in young people with sub-threshold psychotic states[2].

The DSM-5 may also include a new diagnostic criterion for "Mixed Anxiety Depression", in which the patient has three or four of the symptoms of major depression (which must include depressed mood and/or anhedonia) accompanied by anxious distress (which must include two or more of the following symptoms: irrational worry, preoccupation with unpleasant worries, trouble relaxing, motor tension, and fear that something awful may happen). These symptoms must have lasted at least two weeks with no other DSM diagnosis of anxiety or depression present, and both must occur at the same time. There is some obvious face validity to this construct, which benefits from wide acceptance by practicing clinicians and depression researchers, who have long noted anxiety as a predictor of poor response to antidepressants[3] and future suicide behaviour[4]. Obviously, there is a need for effective treatments for comorbid anxiety in both unipolar and bipolar depression, and many depression clinical trials have already began permitting subjects with comorbid anxiety diagnosis/symptoms

into treatment trials, and vice versa. This novel categorisation may promote drug discovery, as well as a re-examination of existing drug candidates such as prazocin, modanfinil and n-acetyl-cysteine, which have all shown some utility in alleviating mixed anxiety and depression symptoms.

A last example of the many proposed revisions to DSM includes the recommendation that the category "Delirium, Dementia, Amnestic and other Cognitive Disorders" be divided into three broader syndromes: "Delirium", "Major Neurocognitive Disorders", and "Minor Neurocognitive Disorders", with no mention of Dementia. In order to meet diagnostic criteria for major neurocognitive disorder, objective assessments must show clear deficits in the relevant cognitive domain (typically > 2.0 standard deviations below the mean of an appropriate reference population), while minor cognitive disorders would be characterised by mild deficits during these assessments (typically 1 to 2.0 standard deviations below the mean of an appropriate reference population). This would require the validation of novel neuropsychological tests (and accompanying independent functional impairment measures) with acceptable sensitivity and reliability, as well as standardised statistical methodologies for choosing relevant cognitive domains. This new classification could sanction the long sought-after indication of "Mild Cognitive Impairment", and expand the development of various nootropics designed to enhance cognition across an assortment of minor cognitive disorders that could be targets for new drug treatment claims.

As a final point, it should be noted that there has been a long evolution of labelling for psychiatric drugs that has been implicitly tied to ever-changing diagnostic classification systems, and international regulatory agencies will undoubtedly need to consider future arguments of new drug treatment claims and outcome measures based on DSM-5. However, this evolution is guided not only by changes in diagnostic classification, but also by relevance to public health, the practice of psychiatry, and clinical meaningfulness to the patients[5].

References:

1. *American Psychiatric Association DSM-5 Development Website DSM-5: The Future of Psychiatric Diagnosis. http://www.dsm5.org/Pages/Default.aspx, visited on November 3, 2010.*
2. *Amminger G.P., Schäfer M.R., Papageorgiou K., Klier C.M., Cotton S.M., Harrigan S.M., Mackinnon A., McGorry P.D. & Berger G.E. Long-Chain Omega-3 Fatty Acids for Indicated Prevention of Psychotic Disorders: A Randomized, Placebo-Controlled Trial. Arch Gen Psychiatry. 67(2), 146-154 (2010).*
3. *Fava, M., Rush J., Alpert J.E., Balasubramani G.K., Wisniewski S.R., Carmin C.N., Biggs M.M., Zisook S., Leuchter A., Howland R., Warden D. and Trivedi M.H. Difference in Treatment Outcome in Outpatients with Anxious Versus Nonanxious Depression: A STAR*D Report. Am J Psychiatry. 165, 342-351 (2008).*
4. *Pfeiffer, P., Ganoczy D., Ilgen M., Zivin K. and Valenstein, M. Comorbid anxiety as a suicide risk factor among depressed veterans. Depression and Anxiety. 26(8), 752–75 (2009).*
5. *Mathis, M. Regulatory Perspective – DSM-5 and drug development. Session presented at the International Society for CNS Clinical Trials and Methodology 2010 Autumn Conference. Oct. 14, Baltimore, MD. 2010.*

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Patient Recruitment: Finding Willing Participants

PEER REVIEWED

There has been much written about the current state of patient recruiting across every major publication, website and blog that focuses on clinical trials and drug development. All elaborate on how critical recruiting the right patient population is to the success and timely completion of a clinical trial. Invariably all focus on the lagging enrolment rates. Much is said about the declining participation in clinical trials due to the high level of patient care in the developed world, as well as the declining participation of investigators in clinical research. In the US, clinical trial participation has dropped to 2% from 4% of the total population. The growth rate of investigator participation in the US was 10% in the 1990s; it is 2% currently. One-third of clinical investigators drop out of drug research every two years.

Delays in completing clinical trials are costly. Companies lose patent exclusivity since there is a finite time window from, in the case of the US Food and Drug Administration (USFDA), the filing of investigational new drug (IND) to the patent expiration. With the clock ticking and time running out, companies potentially lose millions of dollars each day approval is delayed. Pharmaceutical companies are also reportedly spending 60% of their R&D capital on clinical trials. More delays in completing clinical trials lead to more costly clinical trials, further bleeding R&D capital.

According to the Tufts Center for Drug Development (CSDD.TUFTS.EDU), 90% of all clinical trials are delayed an average of six weeks, and only about 7% of all sites deliver what they proposed in the feasibility assessment.

Within this space is the pressure brought on companies to provide more robust and detailed data. More robust data require more patients to be recruited, to ensure a sufficient number of patients pass more stringent inclusion and exclusion criteria.

Table 1 shows the average number of patients enrolled in a typical Phase III registration trial for a mainstream therapeutic candidate today, as compared to 10 years ago.

The quest for naïve patient populations and willing participants in clinical trials has led many sponsors of clinical studies to look offshore for conducting part or all of a clinical trial. For the first time, more clinical trials are being conducted outside of the US than inside the US. In the following fragment of the first sentence of this paragraph "…naïve patient population and willing participants…", the "willing participants" are the key to striking a vein of promising patient candidates. While naïve patients are certainly attractive, they don't necessarily help enrolment rates. Willing participants do.

Table 1 Enrolment numbers for a mainstream therapeutic candidate

	10 Years Ago	Today
Number of patients in a typical Phase III registration trial	2000	5000 to 10,000

Concentrating less on traditional patient recruiting techniques such as investigator databases, community outreach and print, radio and TV advertising, and shifting to internet marketing and social media are other ways to find willing participants.

The rest of this discussion is centred on finding willing participants. The first part focuses on global clinical trials and the search for patients, while the second part focuses on internet marketing techniques

Global Clinical Trials

Low enrolment is the major factor that causes delays in completing clinical trials. This is especially true in the developed world (primarily the US, the EU, Canada and Japan), where patients receive the best medical treatment and there is not a strong desire to participate in a clinical trial, unless one feels it is the only means of getting the best medical treatment for a particular illness. Completing a clinical study on time can save millions of dollars in patent-protected sales revenue. The clinical research markets of countries in the developed world are saturated. Pharmaceutical and biotech companies will benefit enormously if they place clinical trials in countries in Central and Eastern Europe (CEE) and India.

In CEE, the hierarchical structures of the health delivery system (large regional hospitals that treat ailments within therapeutic areas for a given geographic region) direct large patient populations to a single centre. Patients themselves are willing participants since this may be the best medical treatment that they will receive.

On the negative side, some countries within CEE have long approval processes. For example, some regulatory authorities meet infrequently, thus delaying critical study start-up dates. This is a particularly acute problem for Phase I BA/BE studies for generic drugs. The brief patent exclusivity for the first generic drug is lost. This is not as much a problem for later phase studies, where the delay in the study start-up is often more than made up for with aggressive enrolment rates during the conduct of the study.

India, with its large naïve patient population and growing pharmaceutical industry, is a promising area for conducting clinical studies. India is moving forward in all areas, from strictly generics and outsourcing back-office operations, to drug discovery, late pre-clinical development and conducting late-stage clinical trials. With English being widely spoken, there are few language barriers for multinational companies conducting clinical trials in India. Physicians, research coordinators, CRAs and data managers are being trained in good clinical practice (GCP). The sheer size of the population, and this growing knowledge-base in pharmaceutical research and development, flow of capital and global connectivity, have lowered the resistance to conducting clinical trials in India. Here is a population willing to participate in clinical studies that can be mined for

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the volumes of data required for regulatory approvals.

Patient Recruiting and the Internet

The internet is a revolution that has had significant impact on our daily lives. In the narrow area of media advertising, the fundamental shift is from "casting a wide net" to bring in qualified leads, to drawing qualified leads to you in a more focused manner by increasing the visibility of links to a website landing pages in search engine result pages (SERP) through paid placement and search engine optimisation (SEO). With regard to patient recruitment, internet advertising, paid placement and SEO are a means to find the "willing participants". Visible placement of links to website landing pages on SERP draws people who are actively looking for information about a condition they have. This is an important concept. Whereas historical databases have a large volume of patient data, perhaps gleaned from laboratory data, previous clinical studies and insurance claims, a well-placed web page will capture a

more dynamic patient population - patients actively seeking answers and treatment for their illness (or family members and friends seeking answers and treatment on their behalf).

Some more discussion is required with regard to what patients are looking for. Many people do not know what a clinical trial is. They are looking for treatment for their illness, not necessarily to participate in a clinical trial. Thus once they are brought to the website landing page through the visible link on the SERP, they must not be lost. The website must have content that educates the patient about participating in a clinical trial, such that if the patient is willing to participate, he will either call a phone number that is provided or leave his contact information online. Needless to say, there must be compliance with patient privacy regulations and ethics committees and institutional review boards.

Table 2 gives a side by side comparison between traditional recruiting methods and internet-based recruiting.

Table 2 Traditional recruiting compared to internet-based recruiting

Traditional Recruiting	Internet-Based Recruiting
• The sponsor initiates the search for study participants	• Potential study participants initiate the search for their treatment
• Cast a "wide net"	• Narrow search
• Expensive advertising budgets	• Lower cost advertising

Conclusion

The key point discussed here is finding the "willing participants". One approach is to conduct trials in parts of the world where patients are more likely to participate in a clinical trial since they may not be receiving adequate treatment for their illness. Given the growing number of qualified clinical research professionals, adequate facilities and breaking down traditional barriers through global connectivity, conducting trials in developing regions of the world is becoming more feasible.

Recruiting patients for clinical trials utilising internet marketing techniques is a solution for the developed world, where it is becoming difficult to recruit patients to meet the demand for more robust data requirements of regulatory authorities. Here the internet captures patients in that narrow window of time when they are actively seeking answers and treatment for their illness, when participating in a clinical trial may be an option they would consider.

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A Snapshot of the Clinical Trial Experience in South Africa

Africa as a continent for clinical trials is truly emerging. This article will describe some features of Africa in general, and specifically the situation in South Africa.

Africa is a vast continent, with an area of 30 million km2 and a population of 900 million people. The area is three times larger than Europe and the population nearly twice that in Europe.

There are significant differences between various countries in terms of the development of a framework for clinical trials. South Africa is so far the most advanced for clinical trials on the continent. Uganda, Kenya, and Nigeria are examples of countries that are well underway to structuring a clinical trial landscape. Many countries in Africa have not yet embarked on the road of clinical research. Madagascar is an example of this, with its highly conserved genetic pool.

The disease panorama in Africa is one of great variety. HIV/AIDS, tuberculosis (TB), malaria, trypanosomiasis (sleeping sickness) and visceral leishmaniasis are examples of diseases with particular significance in Africa. Infectious diseases in general pose a large problem, together with syndromes connected with diarrhoea. Cancers in both adults and children are common. Other examples are diabetes and cardiovascular diseases.

Initiatives to build a common regulatory framework for clinical trials in Africa are underway[1]. The AfroGuide is an initiative between the UN Economic Commission for Africa, the African Union (AU) and the Good Clinical Practice Alliance, to shape a scientific, regulatory and ethical infrastructure in Africa.

The aim of the project is to provide a collaborative effort for identifying the needs of African countries for guidelines in clinical trials and other areas of health research[2]. It involves an African guideline for Good Clinical Practice, an African Declaration on Ethics in Health Research (involving children) and an African model law on health research. Follow-up meetings are held for planning deliverables of this initiative (Addis Ababa, Nov 2008).

Training in GCP of investigators is conducted in Africa in order to successfully run studies on behalf of sponsors. One such initiative has taken place in Malawi. Training in GCP with particular focus on informed consent has been conducted during the last years. The College of Medicine at the University of Malawi has started a monitoring programme of academic trials and training courses focused on the fundamentals of running clinical trials[3].

Another item of great importance will be the vocational training of new generations of clinical trial managers and monitors.

New technology will facilitate the implementation of international clinical trials in Africa. EDC solutions using mobile technology will be particularly important[4]. Another technology in use in Africa is the digital pen and paper[5].

A biobank unit designed to support clinical trial science research across Africa has also recently been described in this journal[6].

Myths about Africa are abundant. They include unfavourable disease profile and lack of facilities for clinical trials. As myths are replaced by facts, and domestic African CROs enter the scene of the clinical trial landscape in Africa, this will change[7].

The article below describes the status of clinical trials in South Africa today, including an overview of the IP situation.

Background to South Africa Disease Profile (Dr Nirvana Pillay)

South Africa is a multi-cultural society that celebrates diversity in its population of an estimated 49.99 million. The South African population consists of four ethnic groups, with approximately 79.4 % African, 9.2 % Caucasian, 8.8 % Mixed Ancestry and 2.6 % Indian and Asian[1]. Socio-economic inequalities between populations and disparate access to healthcare have led to a spectrum of disease seen in South Africa's citizens today.

Populations in economically-challenged sectors, where education and living conditions are poor, are more susceptible to infectious diseases such as HIV/AIDS and TB. In more affluent populations of the society, diseases such as hypertension, diabetes, obesity, cardiovascular diseases and Alzheimer's disease are more prevalent.

This dichotomy of "first-world" and "third-world" disease profiles within the South African population provides an opportunity for a range of clinical trials to be undertaken within a cultural framework.

Resources

South Africa has a strong medical infrastructure, and consists mainly of public hospitals and about 200 private hospitals. The mining industry also provides its own hospitals and clinics, and there are about 60 countrywide[2]. South Africa has many world class academic centres with qualified investigators and robust telecommunication systems.

Regulatory Framework and Process

Clinical trials on human participants conducted in South Africa must comply with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (SA-GCP)[3]. These guidelines are conducted in accordance with the Declaration of Helsinki, October 2000 and the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, May 1997.

The SA-GCP protects all its citizens, but particularly trial participants from vulnerable communities. These ethical guidelines include 1) respect for the dignity of persons, 2) beneficence and non-maleficence, and 3) justice. These principles guide the relevance and appropriateness of the study rationale, study design, investigator competence, a risk-benefit analysis for participants, transparency, patient informed consent, and privacy.

Before implementing a clinical trial in South Africa, a sponsor or principal investigator must apply to the Medicines Regulatory Authority (MRA) or the Medicines Control Council (MCC) for approval. All clinical trials must also receive ethical approval from

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an accredited research ethics committee based in South Africa. Once approved, the trial information is sent to the Department of Health, where the trial is recorded on the South African National Clinical Trials Register (SANCTR).

Roles

Principal Investigators (PIs)

PIs should be based in South Africa, and are solely or jointly responsible for the study design, study conduct, delegation of trial responsibilities, analyses and reporting of the trial. The accountability of the PI is to the sponsor and regulatory authorities. For multi-centre trials local PIs are mandatory. The competence of the PI and other investigators are based on technical expertise and their humanistic approach.

Sponsors

There has been a disinvestment in clinical research by publicly-funded programmes in South Africa over the past 20 years, and many clinical researchers have turned to pharmaceutical companies for funding of those clinical trials. Consequently, South Africa has a history of performing high-quality clinical trials for major global pharmaceutical companies.

Monitors

Monitors are involved in routine monitoring of quality control functions, and ensure that the Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Pharmacy Practice (GPP) and other guidelines are followed in accordance with the approved protocol.

Auditors

Auditors are independent individuals chosen by the sponsor and/or the regulatory authority to check for compliance of the protocol and regulatory requirements.

Inspectors

Inspectors from the MCC are sent out to clinical trial sites where there is a major violation of GCP or malpractice suspected. These may or may not be scheduled inspection visits.

Patients

Patients in South Africa are highly compliant, and a major portion of the population is treatment-naive.

Sometimes there is a language barrier between the patients and the healthcare personnel. This is overcome with translation of the informed consent form into the cohort-specific language. However, with literacy rates being low in some populations, it is essential that personnel are able to speak the cohort language to ensure proper ethical consent, since most patients in vulnerable communities are compliant and participate to gain access to adequate treatment management and medical care.

Advantages and Limitations

The diversity of patients in South Africa offers a host of clinical conditions ideal for inter-ethnic comparisons and genetic studies. Although there are 11 official languages, English is the most common language spoken in the scientific, business and government communities. South Africa has an already-established medical infrastructure, skilled personnel and robust telecommunication systems conducive to a high-quality clinical research environment. As required by the MCC, all investigators are trained in GCP before participating in clinical trials. South Africa is an ideal destination for seasonal conditions or respiratory disorders, since the seasons are the opposite of that in Europe and the USA (northern hemisphere). This allows for continued progression of the clinical trials, and could possibly shorten the time to market. Furthermore, South Africa has a cost advantage compared to studies conducted in Europe and the USA. The cost is about 25-50 % cheaper at favourable exchange rates.

Despite the many advantages of clinical research in South Africa, the most limiting factor is the time required to gain regulatory approval for trials to begin. South Africa has a stringent regulatory process which is advantageous to sponsors, but the review and approval process is about 14 weeks from the time of a completed submission. After the original submission to the MCC and a one-week validation process to check if all documents are submitted, the clinical trial committee (CTC) will then meet to discuss the application about five weeks later. After a further five weeks the MCC meet to discuss the outcome of the application.

The average maximum length to gain approval for clinical trials reached about seven months in 2008. However, recently there has been a revamping of the MCC regulatory process with the aim of shortening the length of time for processing applications.

Patents in South Africa (Bastiaan Koster)

Registered patents can be obtained relatively quickly in South Africa. On the other hand there are currently long delays in examining new patent applications at the three major patent offices, namely those of the United States, the European Patent office, and Japan. It is not uncommon for delays of up to three years after filing before the first examination report is received. Patent offices and governments are looking at these delays and are in the process of trying to find solutions. The delays are obviously not good for the patent system. Patent applicants are normally anxious to get registered patent rights as soon as possible to enable them to protect their intellectual property. On the other hand, delays in granting patents bring uncertainty to third parties who do not know whether the specific technology will be protected by a patent.

The delays are mainly the result of an increase in the filing of patent applications, as well as the complexity of inventions for which patents are sought. Inventions have become more complex than a number of decades ago, with the result that patent specifications are longer and as a rule more difficult and time-consuming to examine.

Concerns have been expressed in the United States that the delay in examining and granting patents is holding back the recovery of the United States economy. Due to the current delays, start-up companies are not in a position to obtain granted pat-

ents for their inventions within a reasonable period. This has the result that financial institutions are loath to lend start-up companies money without registered patent protection in place.

South Africa has a non-examining patent system. There is therefore no substantive examination in South Africa, and applications are only examined as to formalities. In the normal course of events, a patent application in South Africa will be accepted six months after filing. The application is then advertised, which normally happens two to three months after acceptance. As from the advertisement date the patent is deemed to be granted. It is even possible to request accelerated acceptance at the filing of a South African patent application. The application can then be accepted within a month or so after filing. The result is that South Africa is a jurisdiction where granted patent rights can be obtained very quickly. The enforcement of patents through the High Court in South Africa works well. A dedicated High Court judge who acts as the "Commissioner of Patents" is appointed. While judges usually do not have a technical background, there is an effort to appoint judges who have experience in patent matters. While there is a moratorium of nine months after the granting of a South African patent during which legal proceedings cannot be instituted against third parties, it is possible to bring an application to the Commissioner of Patents to shorten this period. Despite this nine-month moratorium, South Africa is a country where patent rights can be obtained quickly. In addition, the South African legal system in respect of the enforcement of patents is well-established and works well.

Protection of Traditional Knowledge and Traditional Medicines

The debate regarding the protection of traditional knowledge, traditional cultural expressions and genetic resources is ongoing at the World Intellectual Property Organisation (WIPO). Ten years ago WIPO established a committee to consider the issue. The committee is known as the Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore (IGC Committee). While in the early meetings of the IGC Committee some progress was made, no substantial progress has been made during the last few years. One of the stumbling blocks is finding an acceptable definition of "traditional knowledge". There is also an ongoing debate between developing countries requiring an "international legally binding instrument" to deal with the protection of traditional knowledge, and developed countries who believe that it would not be possible to have such an international legally binding instrument due to the complexity of the issues relating to the protection of traditional knowledge.

South Africa has also looked at this issue. In January 2008 a presentation was made to the South African Parliament to present the "Policy and Bill on Protection of Indigenous Knowledge through the IP System". The policy framework and draft bill were published in the Government Gazette of May 2008 and public comment was invited. Much criticism was raised against the proposed bill. In 2008 the bill was withdrawn from the Parliamentary agenda. Inter-departmental consultations followed, and the bill was put on the Parliamentary agenda for 2010. In January 2010 officials of the Department of Trade and Industry briefed the Parliamentary Portfolio Committee on the bill, and it is expected that the bill will be introduced to the National Assembly towards the end of 2010. It is currently unclear what will happen with the proposed bill.

Unfortunately finding a solution for the appropriate protection of traditional knowledge, traditional cultural expression and issues like traditional medicine are not easy, as has been demonstrated by the ongoing international debate at the IGC Committee.

Conclusion

Although the cost of clinical trials is lower in South Africa than in industrialised countries, less than 1 % of global clinical trials are undertaken in South Africa. With attributes of a high-quality clinical research environment, good capacity for multi-ethnic research and high recruitment rates, biotechnology and pharmaceutical companies can benefit from the many advantages that South Africa has to offer.

Furthermore, registered patents can be obtained quickly in South Africa, and the South African legal system in respect of the enforcement of patents is well-established and works well.

References

1. F. Crawley, JCS, Nov 2008, 2. Available at www.afroguide.org
3. J. Jones, JCS, Sept 2008, 4. R. Young, JCS, Sept 2008
5. U. Fröderberg, JCS, May 2009, 6. J. Trusler & P. Mewes, JCS, Nov 09
7. A. Ikeme, JCS, Sept 2009, 8.Statistics South Africa. Mid-year population estimates 2010. Available at http://www.statssa.gov.za/publications/P0302/P03022010.pdf, 9. Healthcare in South Africa. Available at http://www.southafrica.info/about/health/health.htm, 10. Department of Health. Guidelines for Good Practice in the conduct of clinical trials in human participants in South Africa. Available at http://www.doh.gov.za/nhrec/norms/gcp.pdf
11. Gevers W. Clinical research in South Africa: a core asset under pressure. The Lancet, volume 374, issue 9692, pages 760-762.

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Central or Local IECs: Current Situation in Argentina

Recently, in a Perspective article published on October 13 by the New England Journal of Medicine[1] , Jerry Menikoff, director of the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) of the US, wrote about multiple IRB reviews for a single study, and he stated that there is little evidence that such multiple reviews have led to the ethical improvement of protocols or consent forms. Moreover, he pointed out that this practice seems to pose a significant risk of diminishing studies' ethical integrity. Finally, he says that fortunately, some ways of changing this system are being explored. One of the possible solutions for this problem is the use of centralised review by just one IRB/IEC for many institutions, usually by for-profit entities that are independent of the institutions in which the research takes place. These are currently known as "independent" IRBs.

The controversy surrounding this issue, and the evaluation of the pros and cons of the two approaches, is not new. Indeed, the use of central/independent IRBs in the US has about 30 years history. For example, the Western IRB, conducted by Dr Angela Bowen, established the current for-profit structure in 1981, allowing them to give services to their local community and across the United States, and offer institutional IRB services in 1996.

For these reasons, in 1998, the Office of Inspector General (OIG) of the HHS published a few reports about this issue[2,3], . In these documents, it is said that central IRBs offer advantages that institutional IRBs find difficult to match, such as being able to provide unified reviews for multi-site trials, being geared to quick decisions on research plans, and providing a detached source of expertise. But the use of these central independent IRBs raises concerns, e.g., they are not local review bodies, they may be subject to conflicts of interest, and they heighten concerns about IRB shopping.

Regarding the use of local IRBs, the risks described are that they review too much, too quickly, and with too little expertise, and that such multiple reviews by multiple IRBs can result in unnecessary duplication of effort, delays, and increased expenses in the conduct of multi-centre clinical trials, as well as providing little training for investigators and board members. They conduct minimal continuing reviews of approved research, and they face conflicts that threaten their independence.

To help resolve some of these problems, the FDA proposed, in 2006, a guideline for the centralised review process for clinical trials[4].

In academic publications, the use of a single review has been proposed by E. Emanuel and colleagues. Specifically, they proposed mandatory single-time review for multi-centre research protocols, with liability protection for local institutions[5]. Additionally they have proposed abandoning institution-based review and consolidating all independent reviewing, monitoring, training and ethical policy formulation into a system of approximately 20 regional ethics organisations (REOs) for the entire United States[6]. Each research study would be reviewed by only one protocol review committee. For multi-site trials, approval by one REO in the principal investigator's home region would count as sufficient for all participating sites, even sites outside the REO's geographic region.

However, the debate did not end, basically regarding the conflict of interest issue. T. Lemmens and C. Elliot have debated with E. Emanuel[7]. In the opinion of Lemmens and Elliot, these for-profit IRBs have a fundamental conflict of interest, because they are in a client-provider business relationship with the commercial entities whose studies they review. On the other hand, Emanuel says that the critics of these independent IRBs come from the thinking that for-profit companies are necessarily worse than not-for-profit organisations doing similar activities, and that the crucial question is whether an IRB, regardless of its tax status, is performing the ethical review of research at a high level of quality. Emanuel points out that there are absolutely no data showing that either independence of reviewers or quality outcomes are correlated with an IRB's profit status, and there is some real evidence in the regulatory actions and accreditation that the quality of for-profits is as good as, or better than, many of their not-for-profit academic counterparts.

Later, R. Macklin[8], evaluating the independence of both types of boards, expressed that it is not clear which one has the greater conflict of interest: the for-profit IRBs with an interest in maintaining the pharmaceutical industry clients happy; or the committees from the institutions, where their friends and colleagues conduct research, and institutions earn money for the research conducted by them.

Regulatory Environment

In different countries, the law has not required that each institution has its own ethics committee. As we have discussed, in the US, although the presence of IRBs is more common, extra-institutional committees are frequently found.

In Europe, the subject matter of the committees' location is not raised by the regulation[9]. However, the European Directive indicates that to conduct a study throughout the territory, it is sufficient to have the approval of a committee per country.

In Latin America, there is disparity. As an example, in Peru and Brazil, the regulations indicate that the institutional local committees should approve the studies, and if they do not have one, the study can be submitted to the committee of another institution. A very particular case is Chilean regulation. Under this legislation, 28 extra-institutional committees dependent on the various official health services have been created. It is mandatory for these extra-institutional committees to evaluate all the research studies of the region. Although they have been criticised for their delay in evaluating and for the political dependence of the appointment of their members, this system seems to be, in general, the closest to the European model, and to the English one in particular.

The Situation in Argentina

Although up to now the regulation in Argentina allowed the existence of independent IRBs, recently the situation has changed. Under ANMAT Provision 5330/97, independent IRBs were permitted. But the new regulation, ANMAT Provision 6677/10 which came into force last November 5, states (point 4.1.2) that if the site does not have its own committee, it can be replaced by the ethics committee of another institution, with the written agreement of the first institution.

Probably the most stringent situation regarding this issue is the situation in Buenos Aires Province, one of the Argentinean states. The research in human beings in this province is controlled by a law initially released in 1990 , which recently came into force during 2009 . Article 36° and subsequent of this law and regulation stated that in every institution where research is conducted, an ethics committee and a research committee must work continuously, but that the Ministry of Health can set exceptions using these articles, and allow the possibility of independent for-profit committees to participate.

Faced with this decree, the CICOP (labour union of physicians of the province) released a statement indicating that only institutional ethics committees from the province itself might review research studies conducted in the province, and if the institution does not have its own committee, the research might not be conducted there . The suggestion was taken into account by authorities of the Central Ethics Committee of the Province (authority for ethics committees established in December 2009) who have pointed out that, by March 2011, every institution would have its own committee.

Conclusions

Taking into account the controversy surrounding the for-profit committees, the 40-year experience of the IRB system in the US, and the concerns expressed by Menikoff, it is expected that local authorities will allow the use of centralised committees, but not for-profit ones, in order to establish an efficient system to protect human research subjects.

References

1. *N Engl J Med 363;17 NEJM.1592 org October 21, 2010*
2. *OEI-01-97-00192 Institutional Review Boards: The Emergence of Independent Boards OIG, June 1998*
3. *OEI-OI-97-00193 IRBS: A Time For Reform OIG, June 1998*
4. *FDA Guideline Using a Centralized IRB Review Process in Multicenter Clinical Trials. March 2006*
5. *Emanuel EJ, Wood A, Fleischman A, Bowen A, Getz GA, Grady C et al., Oversight of Human Participants Research: Identifying Problems To Evaluate Reform Proposals Ann Intern Med. 2004;141:282-291.*
6. *Wood A, Grady C and Emanuel EJ. Regional ethics organizations for protection of human research participants. Nature Medicine Vol 10: 12 1283-88 Dec 2004*
7. *PLoS Medicine July 2006 Volume 3 Issue 7 941-44*
8. *Macklin R. How independent are IRBs? IRB: Ethics and Human Research 30:3 May-June 2008 15-19*
9. *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. On the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.*
10. *Law 11044/1990, Human Health Research*
11. *Decree 3385, 30 December 2008.*
12. *CICOP For a regulation that guarantee patients Rights. 18 August 2009*

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Think Medicine – *Think India*

India is undisputedly an acknowledged leader in the global pharmaceutical industry (other than drug discovery) measured by any yardstick, such as the number of facilities filing DMFs, facilities inspected by the USFDA, the number of patent challenges, or the volume of APIs & formulations exported, etc. In spite of considerable achievements, several untapped business segments and markets exist, and the room to enhance the country's pharmaceutical exports is vast. Sophisticated chemistry capabilities, lateral thinking abilities in developing non-infringing processes, a disciplined approach to stringent guidelines and a dedication to manufacturing excellence are among the factors which make India a favourite destination to source or outsource various components of the value chain.

A number of leading drugs go off-patent every year, and the generic pharmaceuticals penetration is increasing in all the countries of the world, further raising the opportunity for exports in this segment. Approximately US$123 billion worth of generic products are at risk of losing patents by 2012. Even at a conservative estimate of 15% opportunity, this translates into US$18.4 billion opportunity for India. Intense science, a good understanding of patents and manufacturing to the stringent requirements of the access regime are key requirements for future success in this opportunity. India has the requisite capabilities. Hitherto most opportunities emanated from synthetic chemistry. The opportunities in biopharmaceuticals will be the major attraction in the next decade. New technologies and enhanced regulatory requirements are changing the rules of the game, making production migrate east.

The global market for contract manufacturing of prescription drugs is estimated to increase from a value of $26.2 billion to $43.9 billion. India and China could potentially account for 35 to 40 percent of the outsourced market share for active pharmaceutical ingredients, finished dosage formulations and intermediates. Costs of clinical trials in India are around one-tenth of their levels in the US, and it is estimated that they could be worth US$300 million to India by 2010. There has been a great deal of interest in alternative remedies for some time now. The world market for natural products is estimated at US$62 billion, and is exhibiting double-digit growth rate.

India, with its significant advantage of low cost of innovation; low capital requirements and lower costs in running facilities; well-established manufacturing processes and R&D infrastructure, is strategically positioned to emerge as 'health keeper' of the world. Third world countries are increasingly looking towards India as an alternative source for affordable medicines to solve their increasing healthcare costs. The recent antiretroviral revolution to help millions of AIDS patients in the world was possible only due to India, which is clearly acknowledged worldwide.

The pharmaceutical industry can help India transform itself into a knowledge-driven economy with firm roots in science and intricate knowledge of production and manufacturing engineering. The industry has risen in importance from a sector to an important part of the development process. The country has to look at the pharmaceutical sector as a strategic and flagship industry. The current success is due to amalgamation of R&D (developing non-infringing processes and reverse engineering), manufacturing excellence (designing and running world class facilities with economies of scale), globalisation ability (establishing presence, acquisitions and mergers in the international markets). Such multidimensional excellence will make pharma the torchbearer of the nation, paving the way for R&D-led global market leadership in various goods and services.

India needs a very strong pharmaceutical industry if it has to provide affordable medicines to its over one billion population. The country without strong drug discovery capabilities would be at the mercy of foreign pharmaceutical multinational cor-

porations in the future for new and innovated drugs. The next decade will be crucial in finding a viable strategy to maintain the current dominance in chemistry, to develop biology, and to create drugs that could help the nation.

Today, the whole world acknowledges the supremacy of Indian pharmaceutical capabilities in chemistry, manufacturing and adhering to the stringent guidelines of most advanced nations. In addition to generating revenues and securing appropriate medicines for its citizens, the pharmaceutical industry is propelling the country to emerge as a knowledge economy. Intricate science, technology, legal aspects and regulations involved in the pharmaceuticals industry create a great scientific and business tempo that propels the nation. The diffusion impact of such a knowledge economy will help various sectors to think of global dominance following the example of the pharmaceutical industry, and will provide the means to drive such an achievement. Due to the excellent regulatory and fiscal climate, we have travelled a significant distance. India needs to protect what it has achieved, draw key milestones and road maps, and measure our success with a conscious effort to emerge as an alternative power in the global health sector.

There is another reason to contend that the pharmaceutical industry deserves a greater focus today. A 'brand India' has gradually evolved around the Indian pharmaceutical sector, with the emergence of new segments of the industry, such as contract manufacturing, contract research services, bio-pharmaceuticals and Indian systems of medicines. It is even more necessary that this branding be adequately strengthened. This would require investments in brand-building. It is perceived that government needs to prepare an action plan for brand-building around the pharmaceutical sector. This will also help in creating several spin-off benefits, such as dealing with the problem of counterfeit drugs.

A higher level of innovation and IPR management, coupled with strategic manufacturing and aggressive marketing, will largely determine the Indian pharmaceutical industry's future. Specific measures for strengthening the IPR system with action points for the government, the judiciary and the legal system, industry, the Department of Science & Technology and the educational system have been suggested. Some suggestions for enacting a TRIPS-compatible IPR legislation, which protects the interest of the consumers and allows a platform for the growth of the Indian pharmaceutical industry, have been made.

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Paediatric Pharmaceutical Medicine

Paediatric Clinical Research and Considerations for Clinical Trials

PEER REVIEWED

Children and adolescents suffer from many diseases for which safe and effective pharmacotherapy has been developed for adult patients. However, children may have a disease process that is similar to or vastly different from their adult counterparts. While it has been understood from an intellectual perspective that clinical trial information is critical for this population, two factors have led to a lag between utilisation of pharmaceutical agents and knowledge of their action and dosing in children: growth and development issues, and ethical concerns. Growth and development are under way at precisely the time the pharmaceutical agent is being given, and this phenomenon continues through adolescence. It is also recognised that this patient population is vulnerable and thus demanding of a cautious approach when they participate in clinical trials. It is well understood, therefore, that children are unique: how to embrace this distinction while developing protocols, protecting safety, and gathering useful data has been the challenge of paediatric pharmaceutical development.

Factors Affecting Paediatric Drug Development

Approximately 20 % of all drug sales are attributed to the treatment of individuals less than 18 years of age. Much of this use is a consequence of off-label prescribing, especially in certain patient populations such as neonates where off-label use is upwards of 90 %.[1] While paediatric drug regimens for younger patients have become well established for some indications, there are many cases in which physicians have to make paediatric prescribing judgments in the absence of safety and efficacy data collected during paediatric clinical trials. These judgments typically concern how best to modify the recommended adult dose for a given paediatric patient.

Of all the pharmaceuticals used in paediatric populations, less than 20 % have been tested in this population in the United States (US), and less than 50 % have been similarly tested in the European Union (EU). These percentages should increase as paediatric clinical development plans are put in place for new therapeutic entities as a consequence of legislation in both the US and EU. However, many pharmaceutical agents that are now "off-patent" have not been, nor are likely to be, studied in paediatric age groups without some incentive by national health services or governments. Therefore, key therapeutic questions involving dose, duration, frequency, and toxicity/safety are very difficult to answer for some agents. This can lead to an excess of adverse drug reactions and less-than-anticipated effectiveness, which itself can legitimately be considered an adverse event.

Paediatric Regulations

Both the US and EU have established specific laws and regulations pertaining to the ongoing clinical development of pharmaceutical agents for children. These regulations apply to agents that are currently under development, but do not cover those that are off-patent. Additionally, although the regulations are similar in many ways, there are differences which should be noted, as listed in Table 1.

Both the FDA and EMA paediatric regulations contain incentives for sponsors, as well as legislatively mandated requirements. Historically, in the US, two separate legislative events supplied the incentive and the requirements. The FDA Modernization Act of 1997 and the Best Pharmaceuticals for Children Act (BPCA) in 2002 provided the incentive. The 1998 Pediatric Rule and the Pediatric Research Equity Act (PREA) in 2003 provided the requirements. BPCA and PREA were reauthorised in the Food and Drug Administration Amendments Act of 2007 (FDAAA), which sunsets in October 2012. The incentives and requirements are unified in the EMA, and all marketing authorisation applications (MAAs) must contain a paediatric investigational plan (PIP) including a waiver or deferral request. If the PIP is not included, the MAA will be denied.

Table 2 presents a list of major paediatric regulatory initiatives, including examples from regulatory agencies and the US National Institutes of Health.

Although collaboration between the FDA and EMA does occur, the requirements for development of a specific pharmaceutical agent may or may not be the same. The agencies may

Table 1: Comparison of FDA Written Request (WR) and EMA Paediatric Investigational Plan (PIP)

FDA Written Request (WR)	EMA Paediatric Investigational Plan (PIP)
Voluntary	Mandatory
Issued by the FDA but Proposed Pediatric Study Request (PPSR), a separate document, requested by the sponsor*	Issued by the sponsor
Age-appropriate formulation statement	Complete statement including age-appropriate formulation and product quality
Waiver/deferral requests not included	Includes waiver/deferral requests
Applies to drugs only	Applies to drugs and biologics
End of Phase II or Phase IV	End of Phase I
Six-month patent extension for on-patent drugs	Six-month patent extension for on-patent drugs

Table 2: Chronology of Major Paediatric Regulatory Initiatives in the US and EU

Year	Event, Consequence(s), and Pertinent Information
1979	FDA issued regulations requiring the addition of paediatric information to drug labels. (This did not result in increased numbers of paediatric clinical trials or improved paediatric labelling.)
1994	FDA released the first of two Pediatric Rules (not laws). This required sponsors to review existing paediatric data for approved drugs, or to extrapolate from adult data. (This did not result in increased numbers of paediatric clinical trials or improved paediatric labelling.)
1997	FDA Modernization Act of 1997 (FDAMA), which granted six-month patent extensions for paediatric testing of drugs already approved for adults. This expired in 2001.
1998	FDA released the second of two Pediatric Rules. This required the paediatric testing of all new drugs potentially used for children. Safety and efficacy data needed to be collected, and supplemental applications were required for new indications. This rule was suspended by a US District Court in 2002.
2002	Best Pharmaceuticals for Children Act (BPCA). This became active following the expiration of FDAMA. It granted patent extensions to sponsors conducting paediatric trials in response to a Written Request from the FDA. Research had to consider racial and ethnic minorities. A new office at the FDA was created to coordinate these activities. The BPCA was set to expire in 2007.
2003	Pediatric Research Equity Act (PREA). This amended the Food, Drug and Cosmetics Act (FDCA) to give the FDA clear authority to authorise research for drugs used in paediatric patients, and required age-appropriate formulations be produced and tested for each age group.
2007	The FDA Amendments Act of 2007 (FDAAA) reauthorised and updated the PREA and the BPCA. This act required that data to support safety and efficacy in all paediatric age groups be submitted for all applications; labels are to include negative or inconclusive results ('label transparency'); and all written requests are to be reviewed by the FDA Pediatric Committee.
2007	The EMEA Paediatric Regulation (EC1901/2006) in Europe required a Paediatric Investigational Plan (PIP), which provided six months of patent protection even if study results are negative.
2010	BPCA Prioritization Process 2010. Conducted under the auspices of the National Institute of Child Health & Human Development (NICHD), this process has been developed to identify gaps in paediatric therapeutics, primarily off-patent drugs that need further study through clinical trials or other avenues of research.

ask different questions and require different protocols. Each agency has a specific review committee assigned to provide input on paediatric clinical development programmes. The FDA's Pediatric Review Committee is a consultative committee that provides recommendations to the various FDA review divisions. The EMA's Paediatric Committee provides reviews of the submitted PIPs. Their role is not consultative as their decisions are binding. As a consequence of the difference between US and EU regulations, clinical development planning for paediatric projects continues to be complicated. However, the overriding objective of both agencies and committees is to avoid subjecting children to unnecessary research and to hasten the development of medicines for children.

Additionally, while ICH globalisation of clinical research principles has been largely achieved across the (traditional) three major pharmaceutical markets of the United States, Ja-

pan, and Europe, paediatric "regulations or provisions are not yet harmonized or even in place across all territories".[1] This lack of harmonisation may further hinder the ability to study and test these agents in children.

Paediatric Clinical Trial Considerations

Aripin et al.[2,3] have reviewed published reports of paediatric randomised controlled trials. Their observations included the following:

- The types of drugs for which the most trials were conducted were nervous system (26 %), anti-infective (17 %), respiratory (12 %), and antiparasitic (8 %) drugs;
- Few studies (7 %) were performed in neonates;
- In many trials that recruited both adult and paediatric subjects, the reports inadequately described the characteristics of the paediatric subjects;
- Only about a quarter of the trials were conducted in low and lower-middle income countries;
- Paediatric randomised drug trials performed in low and lower-middle income countries were of lower methodological quality.

Since the FDA and EMA adopted specific regulations, 394 Written Requests have been filed and 610 Proposed Pediatric Study Requests (PPSRs) received in the US, and more than 200 labelling changes made.[4] In the EU, the 1000th application for a PIP or waiver was received on 10th August, 2010.[5] Despite the complexities of the regulatory environments in the US and EU, therefore, paediatric studies are being completed and new information is being listed on pharmaceutical product labels. However, they still represent only a small percentage of overall clinical trials.

Investigator and Site Considerations

Investigators and their staff at investigational sites need certain skill sets that differ from those used when running adult trials. Since parents/guardians must be involved, both the site facilities and the staff must be subject- and family-friendly. All involved must also be culturally sensitive to in the country (and sometimes even locality) where the trial is being conducted. These considerations are particularly important when birth control and avoidance of pregnancy discussions are occurring. The site must understand the (typical) informed consent process as well as the assent process for those children for whom assent is appropriate. Informed consent discussions must take place between the parent and or legal guardian and the Investigator. The site must have phlebotomists skilled and experienced at taking blood samples from infants, children, and teenagers, and staff who understand and know how to address sexual activity and birth control in this cohort. Probably of greatest importance is the unwavering commitment and enthusiasm of the investigator and site staff for the project being performed.

Study Design and Execution Considerations

It is extremely important that a study design created for an adult trial of a particular drug is not simply modified by changing the age range in the list of inclusion/exclusion criteria. There are many specific paediatric issues that must be considered in the ethical design of clinical trials intended for paediatric populations. These include:

- Phase I trials cannot be conducted on healthy children, but rather must employ patients with the disease or condition of clinical concern.
- The nature of the disease can be different, requiring different endpoints.
- Blood draw volume restrictions differ at the site and country level.
- "Paediatric" patients include neonates through adolescents, with very different considerations for each age group. The FDA age groups are:

o Adolescents: 12-16 years;
o Children: 2 to 12 years;
o Infants: 1month to 2 years;
o Neonates: newborns up to 1 month of age.

- Palatability of the investigational product is a concern.
- The formulation of a drug needs to be different for younger and older patients (e.g. liquid solutions or suspensions, granulation vs. tablet or capsule).
- Laboratory and ECG normal ranges per age group must be used.
- Many trials will need to be conducted internationally, adding another layer of complexity.

Pharmacokinetics

While it is outside the scope of this paper to discuss paediatric pharmacokinetics in detail, a brief overview is necessary to understand the complexities of the various paediatric populations to be studied. Marked changes in body weight and physiological function occur as age increases in the years before adulthood.

Since many physiological differences between children and adults can result in age-related differences in pharmacokinetics, "understanding the effects of age on bioavailability, volume of distribution, protein binding, hepatic metabolic isoenzymes, and renal elimination can provide insight into optimizing doses for pediatric patients."[6] Some changes of particular relevance are:[7]

- Gastric absorption of oral drugs is impacted by the high pH of gastric juice in newborns, and by slow gastric emptying up to six months of age. This generally results in poor absorption (except for lipophilic drugs).
- Intestinal absorption and the protein binding ratio is low in newborns.
- Drug metabolism generally develops quickly after birth and reaches the adult level in two to three years, though there are many exceptions. For example, among the glucuronosyltransferase (UGT) enzymes, UGT1A1 and UGT2B7 reach the adult level by three months of age, whereas UGT1A6, UGT1A9 and UGT2B7 take a few years to ten years.
- The relative liver weight and hepatic blood flow rate per unit of liver weight is larger in children than in adults, affecting hepatic drug metabolism.
- Differential renal influences may also occur.

As a result of these and other maturational influences, newborns, infants and children show different pharmacokinetics for different drugs, meaning that the pharmacokinetics data of each drug should be considered when determining paediatric doses.[7]

Modifying Adult Doses for Paediatric Patients

As Mathis and Rodriguez[8] observed, for many years pharmacotherapy was not explicitly studied in the paediatric population: "The lack of data forced clinicians to treat children using empiric therapy, often guessing at the treatment dose." Additionally, there was no evidence that a drug would be safe and efficacious in this population. As discussed earlier, legislation in the US and EU has impacted this situation favourably, with more drugs having paediatric labelling, and more data on safety and efficacy being available from paediatric clinical trials. Nonetheless, where such information is not yet available, physicians who wish to prescribe drugs to paediatric patients have to use judgment in the choice of dose. In general, there are various dosing guides used by paediatricians and neonatologists, which may or may not include "evidence" for the dose.

Various means of optimising this judgment utilising pharmacokinetic knowledge have been described. The superfamily of cytochrome P450 (CYP) enzymes mediates most drug functional group metabolic modifications, and hence they are important in the study of drug responses. Particularly important enzymes include CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, and CYP3A.[9] Anderson and Lynn[6] reported that "children need weight-corrected doses that are substantially higher than adult doses" for drugs that are metabolically eliminated solely by CYP1A2, CYP2C9, and CYP3A4. In contrast, weight-corrected doses for drugs eliminated by renal excretion or metabolism involving CYP2C19, CYP2D6 and other specific enzymes are similar in children and adults. Other authors have reported computational and model-based approaches to determining paediatric doses based on pharmacokinetic information.[10,12]

Ethical Considerations in Employing Paediatric Subjects in Clinical Research

While ethical considerations are a core aspect of all human (and non-human animal) research[13], attitudes towards and emotions engendered by the participation of infants, children, and adolescents have, until quite recently, been particularly vociferous. More recently, while acknowledging additional protections necessary for children enrolled in clinical trials,[14,18] dispassionate deliberations have focused on ways to surmount ethical challenges and the benefits to paediatric populations of a clinical science-based foundation for paediatric pharmacotherapy.[17,18] As Rose[19] observed:

> The pendulum is swinging away from protecting children against research toward protecting their health through research…Research with children intends to improve the therapeutic armamentarium of pediatricians, physicians, parents, and all child healthcare givers to stabilize and improve children's health and to reduce their suffering when they are ill.

Concluding Comments

The world of paediatric clinical research is evolving quickly. The need for pharmaceutical agents tested in, and labelled for, paediatric populations continues. International harmonisation of regulations and principles of paediatric research would go far to simplify the complicated process currently required. The issues of growth, development, and surmounting ethical challenges will continue to require trained and dedicated individuals to design, conduct, and complete trials in this patient population.

References

1. *Smit-Marshall P, 2010, Pediatric trials: A worldview. Applied Clinical Trials, 19:32-39.*
2. *Aripin KN, Choonara I, Sammons HM, 2010, A systematic review of paediatric randomised controlled drug trials published in 2007. Archives of Disease in Childhood, 95: 469-473.*
3. *Aripin KN, Sammons HM, Choonara I, 2010, Published paediatric randomized drug trials in developing countries, 1996-2002. Paediatric Drugs, 12:99-103.*
4. *http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf (Accessed 20th October 2010)*
5. *http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/10/news_detail_001128.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1 (Accessed 20th October 2010)*
6. *Anderson GD, Lynn AM, 2009, Optimizing pediatric dosing: a developmental pharmacologic approach. Pharmacotherapy, 29:680-690.*
7. *Yokoi T, 2009, Essentials for starting a pediatric clinical study (1): Pharmacokinetics in children. Journal of Toxicological Sciences, 34 (Suppl 2):S307-312.*
8. *Mathis L, Rodriguez W, 2009, Drug therapy in pediatrics: A developing field. Dermatologic Therapy, 22:257-261.*
9. *Wijnen PA, Op den Buijsch RA, Drent M et al., 2007, The prevalence and clinical relevance of cytochrome P450 polymorphisms. Alimentary Pharmacology and Therapeutics, 26:211-219.*
10. *Suzuki S, Murayama Y, Sugiyama E, et al., 2010, Estimating pediatric doses of drugs metabolized by cytochrome P450*

(CYP) isozymes, based on physiological liver development and serum protein levels. Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan), 130:613-620.
11. *Cella M, Gorter de Vries F, Burger D, et al., 2010, A model-based approach to dose selection in early pediatric development. Clinical Pharmacology and Therapeutics, 87:294-302.*
12. *Abernethy DR, Burckart GJ, 2010, Pediatric dose selection. Clinical Pharmacology and Therapeutics, 87:270-271.*
13. *Turner JR, 2010, New Drug Development: An Introduction to Clinical Trials, 2nd Edition. New York: Springer.*
14. *Nelson RM, 2009, Additional protections for children enrolled in clinical investigations. In Mulberg AE, Silber SA, van den Anker JN (Eds), Pediatric Drug Development: Concepts and Applications. Hoboken, NJ: Wiley-Blackwell, 81-101.*
15. *Baer GR, 2009, Ethical issues in neonatal drug development. In Mulberg AE, Silber SA, van den Anker JN (Eds), Pediatric Drug Development: Concepts and Applications. Hoboken, NJ: Wiley-Blackwell, 103-113.*
16. *Nelson RM, Lewis LL, Struble K, Wood SF, 2010, Ethical and regulatory considerations for the inclusion of adolescents in HIV biomedical prevention research. Journal of Acquired Immune Deficiency Syndromes, 54(Suppl 1):S18-24.*
17. *Kölch M, Ludolph AG, Plener PL, 2010, Safeguarding children's rights in psychopharmacological research: ethical and legal issues. Current Pharmaceutical Design, 16:2398-2406.*
18. *Halpern SD, Randolph AG, Angus DC, 2009, No child left behind: Enrolling children and adults simultaneously in critical care randomized trials. Critical Care Medicine, 37:2638-2641.*
19. *Rose K, 2009, Ethical principles of pediatric research and drug development: A guide through national and international frameworks and applications to a worldwide perspective. In Mulberg AE, Silber SA, van den Anker JN (Eds), Pediatric Drug Development: Concepts and Applications. Hoboken, NJ: Wiley-Blackwell, 115-129.*

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Be Prepared for the Challenge of dealing with an Orphan Disease

1 The Challenge

Not only do trials dealing with an orphan disease potentially raise special problems, but also trials with rare patients require a calculated number of patients, none of which must be lost due to documentation failures.

The trial in question comes with two specific challenges: due to the low incidence of patients, the required number of patients can only be reached by a large spatial distribution, i.e. many centres in many countries. This causes an immense organisational effort. At the same time, the study was supposed to accompany the drug's market introduction in various countries and to yield a positive pharmaeconomic argumentation.

Due to the product's market situation and the post-approval late phase, the project is subject to special cost-efficiency requirements imposed by the sponsor. The project organisation had to be designed in a way to guarantee the fulfilment of these requirements.

Currently the recruitment of sites in the various countries has been finalised successfully in time, and the data collection is in progress.

2 Study Setting

The study setting contains a total of 70 centres in Austria, Belgium, Czech Republic, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Switzerland, and the UK. It is planned to include 250 patients in a recruitment phase of 24 months, with the total duration of the project being 58 months. It is a Phase IV study concerning patients in a late stage of a neurological indication.

3 The Three Pillar Regional Service Provider Organisation

The customer expects high quality in a clinical trial, which in this case is combined with the challenge caused by the large spatial extension that was necessary to gain access to the few patients by recruiting a huge number of centres. A big international CRO with affiliates in the relevant countries is well-equipped to conduct such a study, but a large overhead of institutional costs is inevitable. To obtain a reasonable quality-cost ratio, we advised the customer to implement a modern organisational framework, which we call a Regional Service Provider Organisation.

The Regional Service Provider Organisation is based on three pillars:

3.1 Pillar 1: Project Management

The first pillar is built of a global core project management team that is responsible for coordination of the entire project, for the sponsor communication, and for control. This team translates the sponsor's requirements into tasks and process descriptions, and delegates them into the respective organisations. At the beginning of the project, the project management team makes sure all participating organisations are bound by contracts. During the whole duration of the project, the project management team supervises the performance of all involved organisations.

3.2 Pillar 2: Technology

The second pillar consists of a technology platform that is accessible via a standard internet browser. It integrates all participating organisations and persons.

This integration implies that all CROs use this software. In a setting like this, electronic data capture (EDC) is necessary to deal with the logistic overhead. But, unlike the conventional deployment of EDC, not only are the study data collected via EDC, but also all study-related activities. For this purpose, a clinical trial management system (CTMS) has been integrated into the EDC system. This system is used by the project management team described in Pillar 1 to supervise and monitor all process data.

It is crucial that the technology provides a unique platform - that is, a unique source of information - for the collection and documentation of both study and process data. Thus, the collection of these data is mandatory, e.g. the review and approval of monitoring reports.

According to the study setting, the CTMS collects all process data, such as the entire site personnel with their contact data and the bank details of the investigator, as well as the contact details of the local IRBs. It defines exactly the structure of every visit, beginning with the site selection visit and site initiation visit, across the predefined number of monitoring visits, and up to the closure visit. The visit structure contains the documentation of contacts before the visit, all required activities for the visit preparation, such as the return date of the feasibility questionnaire in the case of the site selection visit, and a visit report requesting every required activity, e.g. the ethics committee approval date in the case of the site initiation visit, and a follow-up letter after each visit.

Furthermore, the CTMS collects every contact with the IRBs in each country, the submission date and the subsequent reaction, and the management of the health authorities' approvals.

The project state can be viewed at any time in different overview graphs.

3.3 Pillar 3: CRO

The third pillar consists of the CROs being established independently in the various countries, but work together in the Regional Service Provider Organisation Structure. This structure ensures that

- contractual relationships for the project in question can be established easily between the participating companies at project start
- the companies have implemented unified SOPs

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- general responsibilities within the organisation are already assigned. The project manager only has to assign the contents for the current project.

Such a pre-existing organisation has been involved in this project.

4 Advantages

The interaction of these three pillars ensures a smooth conduct of the projects and yields advantages of know-how, transparency and efficiency that would be harder to achieve with any other solution.

4.1 Local Know-how

In this setting, the national knowledge of the organisational entities in the various countries is implicitly used during the project. This holds not only for the regulatory aspects, but also for the indication-specific aspects. Especially in the management of rare patients and difficult indications, national peculiarities tend to occur, i.e. to what extent are the health and care insurance providers ready to accept the costs for certain positions. Locally-established organisations know these circumstances and can deal with them.

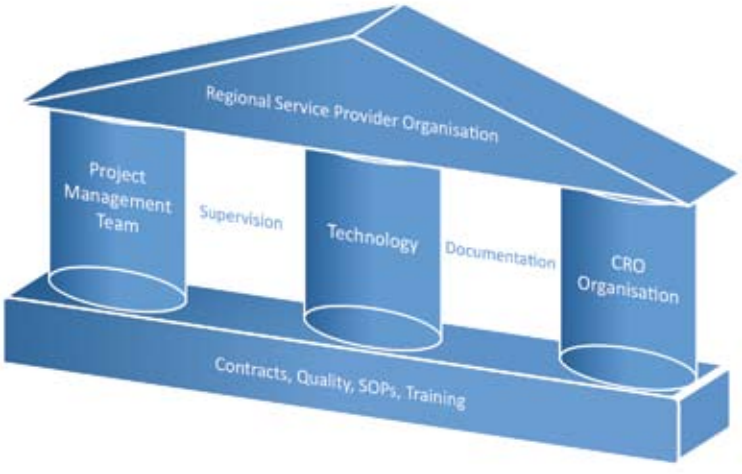
This knowledge is a matter of course for local CROs. It is available to multi-national CROs from a certain company size, but a small CRO with no local affiliates in different countries has no access to it.

Furthermore, it is important to have long-established persons on site who know the respective healthcare system or certain difficulties (e.g. with the reimbursement). These persons know contact partners for all eventualities, and how to convince them.

4.2 Transparency

Multi-national projects pose a challenge in detecting the risks in the action flow in time, and to ensure the observance of the timelines. In our case, by deploying the CTMS, the project management team of Pillar 1 could ensure, and show at any time, that the site recruitment was performed exactly in the time window defined by the sponsor. Every success or failure can be seen and measured at once with such a CTMS. Control measures can be taken immediately as soon as a problem shows up and have an instantaneous impact, which is not the case when quarterly or semi-annual consolidated reports are implemented.

The construction offers special advantages in terms of control. The CROs (Pillar 3) document their activities in the CTMS (Pillar 2). Only the complete and confirmed documentation of an activity triggers the payment. This is how, in a Regional Service Provider Organisation, the compliance of the various organisations is ensured.



Not only does a proven evidence of activities trigger payment, the required activities themselves are strictly defined by the system. The CTMS expects certain documentations. Data other than the expected ones cannot be documented and thus, they cannot be paid. The course of actions is exactly defined in terms of content and time.

The sponsor has access to the tool and can supervise the progress of the project online, and in real time. This is possible because all information concerning the entire complex project is consolidated in only one comprehensive central database. All pre-arranged reports are available directly in the system and do not have to be sent via mail or e-mail. No further data transfer is required.

4.3 Efficiency

Indications with rare patients confront sponsors with the challenge to lose none of these patients while being subject to limited financial resources. Every patient is "expensive", not only regarding the medical treatment, but all the more as he is irreplaceable, because statements with a defined statistical power are required for rare diseases as well.

Thus, the study goal is not only to adjust the medical treatment or to establish a medication in the market, but also to use the existing capacities efficiently in a clinical trial. There are settings in which almost every existing patient has to be included in the trial. Project managers for studies dealing with rare indications know this problem.

A Regional Service Provider Organisation can spread a large net and thus be prepared to efficiently collect even the rare cases by means of a huge geographical extension, and to include them in a clinical trial.

Further more, such an organisation offers intelligent measures to optimise cost-intensive actions. The challenge of the wide distribution of patients (few patients per centre) is likely to raise immense monitoring costs.

- Each monitoring visit causes immediate costs.
- Assuming 1,000 Euros per visit, one single regular visit costs 100,000 Euros in a 100-centre trial.

Such rapidly-spiralling costs can be decelerated by the following measures:

- Deployment of data monitors. The monitor supervises and supports the centre via the system without having to physically visit the centre.
- Deployment of telemonitoring or remote monitoring; telephone contacts and in special cases even remote SDV (source documents can be faxed to the monitor).

Even though the number of physical visits to the centres can never be reduced to zero, these measures can save or optimise one or another visit. An important improvement is the possibility for the monitor to catch up online on the state of the centres before beginning his journey.

Additionally, quality metrics for centres can be introduced. There are different quality indicators such as number of que-

ries, documentation progress, data quality etc. Based on these quality metrics, decisions can be made as to which centres are provided with a higher or lower degree of attention. This enables the intensive support of exactly those centres where it pays off.

In each study there are centres that perform brilliantly, even with little support. These are provided with a minimum of visits and SDV to ensure the adherence to legal regulations. On the other hand, there are centres where even intensive support would not lead to a good result; all the effort would be lost. After all, the monitoring power should be concentrated on centres which are in between these two extremes, and where the monitor has the largest impact. The information required for this method is provided by the deployment of the IT solution in Pillar 2 - without having to visit the centres in the first place. The project management team in Pillar 1 can decide where (in Pillar 3) to draw the monitoring energy. Thus, the monitoring capacities are deployed in a way that allows for their best efficiency.

5 Conclusion and Perspective

Clinical research is heavily under pressure to maintain or even increase quality standards, by simultaneously maintaining or even reducing the costs. Additionally, special indications or clinical settings are facing the challenge to deliver evidence to policy- and decision-makers without the funding that usually is available for the promotion of block-buster drugs.

Usually under these circumstances, vendors sprout promising IT solutions to deal with these new challenges. The past has taught, however, that IT alone does not solve problems. Only the integration of a three-pillar solution consisting of contractual and quality arrangements prepared in anticipation of complex settings under cost pressure, a qualified project management, and finally an appropriate IT infrastructure, provides new and intelligent means to tackle this challenge.

This article highlights the need to be prepared before the challenge occurs, and that organisational and procedural infrastructure based on a homogenous IT solution can tackle all issues arising from these settings. It should additionally confirm that there is no need to be afraid. Medium-sized, localised organisations focused on a sponsor's problem provide all that is needed, and they provide it in a suitable timeframe, and at attractive costs.

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Testosterone Replacement Therapy in Adult Testosterone Deficiency Syndrome: Still a Matter of Debate

PEER REVIEWED

The last 15-20 years have seen rapidly growing awareness of the important role that testosterone plays in maintaining men's health and quality of life. Testosterone deficiency is now recognised as a very real and increasing problem for several reasons. Global aging is occurring rapidly in both developed and developing countries, but unfortunately an increased life expectancy is not being accompanied by greater health expectancy.

The symptoms of aging include tiredness, lack of energy, reduced strength, frailty, loss of libido, decreased sexual performance, depression, and mood change. Concomitantly, with age the testosterone levels fall[1-3] and elderly men with hypogonadism experience similar symptoms. This raises the question of whether some symptoms of aging could be due to relative androgen deficiency. On the other hand, similarities between normal aging and the symptoms of testosterone deficiency make the clinical diagnosis of hypogonadism in aging men more challenging.

International consensus documents have been recently published, by both andrologists and endocrinologists, providing guidances on the diagnosis, treatment, and monitoring of late-onset hypogonadism (LOH) in men[4-5].

Controversy in defining the clinical syndrome continues due to the high prevalence of hypogonadal symptoms in the aging male population, and the non-specific nature of these symptoms. Moreover, as with any other clinical intervention, a decision to treat patients with testosterone requires a balance of risk versus benefit.

Diagnosing Late-Onset Hypogonadism (LOH)

Cross-sectional and longitudinal data indicate that the testosterone (T) falls progressively with age, and that a significant percentage of men over the age of 60 years have serum T levels that are below the lower limits of young adult (age 20–30 years) men[6-9]. The decline of serum T levels appears to be a gradual, age-related process resulting in an approximately 1 % annual decline after age 30.

This has been emphasised by Wu et al. in the European Male Aging Study[9], which shows the complex multiple alterations in the hypothalamo–pituitary–testicular axis function associated with progressive age-related testicular impairment, as well as specific risk factors, and emphasises the importance of maintaining T levels in aging men.

The principal questions raised by these observations are whether older hypogonadal men will benefit from T treatment, and what will be the risks associated with such intervention. In fact, men's health is still in need of urgent attention: the age-adjusted mortality rates for the 15 main causes in the United States reveal that men have higher death rates than women[10]. The reasons for such premature male mortality are not fully understood. Evidence published over the last few decades has pointed out that T itself could play a causal role in lower life expectancy in males. However, studies published in the last three years seem to suggest that the age-associated T decline, rather than the T per se, plays a major role in the higher mortality rate observed in males. Evidences from the Rancho Bernardo study suggest that men, whose total T levels are in the lowest quartile (<240ng/dL, 8.1 nmol/L) at baseline, have a 40 % increase of mortality and 38 % of cardiovascular mortality, in comparison with those with a higher T level[11]. Similar results were also reported in the European Prospective Investigation into Cancer in Norfolk Prospective Population Study[12].

The terms 'testosterone deficiency syndrome' or 'late onset hypogonadism' (LOH) have been used to describe this phenomenon. According to a recent consensus panel, LOH has been defined as "a clinical and biochemical condition associated with advancing age, characterized by specific symptoms and a deficiency in serum T levels".[4] The symptom most associated with LOH is low libido, while other manifestations include: erectile dysfunction (ED), decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. The most widely accepted parameter to establish the presence of hypogonadism is the measurement of serum total testosterone (TT). There is general agreement that a TT level above 12 nmol/l (or 350 ng/dl) does not require substitution, whereas patients with serum TT levels below 8 nmol/l (or 230 ng/dl) will usually benefit from T treatment. If the serum TT level is between 8 and 12 nmol/l (the so-called "grey zone"), repeating the measurement of TT with sex hormone-binding globulin (SHBG) to calculate free T may be helpful.

The measurement of free or bioavailable T (FT) should be considered when the serum TT concentration is not diagnostic of hypogonadism, particularly in obese men. There are no generally accepted lower limits of normal for FT for the diagnosis of hypogonadism. However, an FT level below 225 pmol/l (or 65 pg/ml) can provide supportive evidence for testosterone treatment.[13-15]

Prevalence of LOH: Symptomatic or Asymptomatic?

The prevalence of LOH in different countries is a matter of intense academic debate. Estimates of its frequency in the general community vary as widely as between 0.5 % 16 and, on a symptomatic basis in men over 50, nearly 50 %.17 The answer depends on the population of men studied, their age, and whether symptoms alone are considered diagnostic or additional laboratory criteria such as testosterone level are required.

Large-scale epidemiological studies, such as the Boston Area Community Health (BACH) Survey,17 have shown that while 37.7 % of men over the age of 50 reported symptoms of LOH, only 15 % had low TT, 9.9 % low FT and 8.4 % both. This left

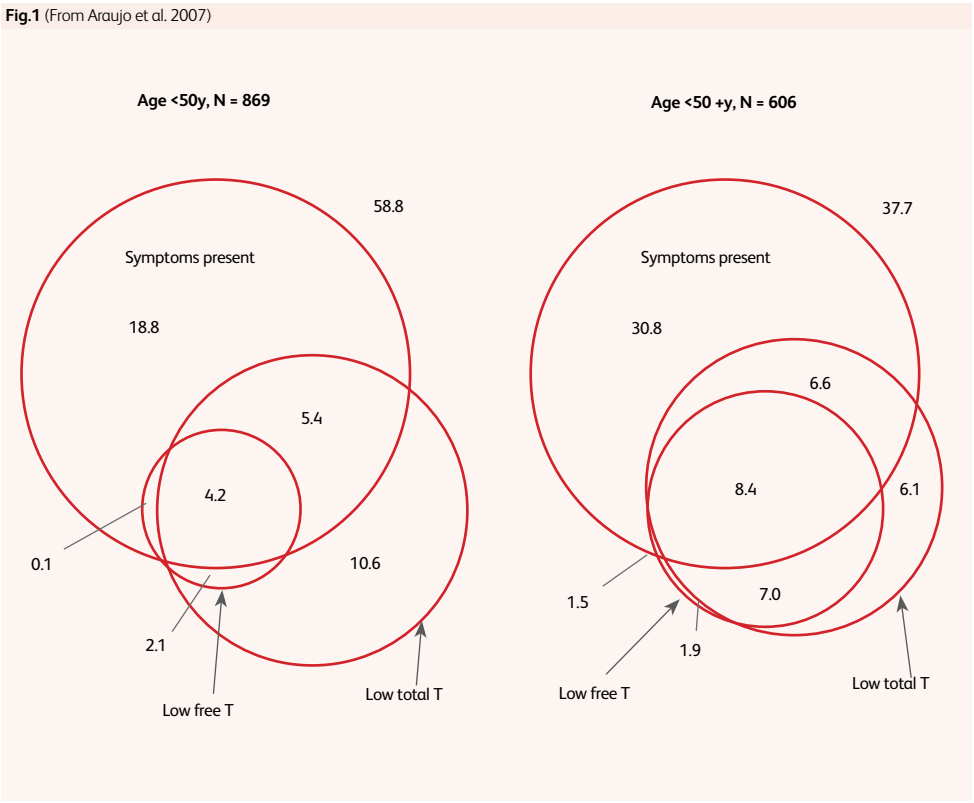
15 % with low levels of TT or FT, and no symptoms. The very poor overlap of symptoms and biochemistry, seen most clearly in Venn diagrams resulting from such studies, raises the question of who should be given access to a therapeutic treatment with T: the patients with symptoms, even if they lack a biochemical passport, or only those with both?

Depicted in Fig. 1 are Venn diagrams showing the inter-relationships among symptoms, low total testosterone [<300 ng/dl (10.4 nmol/litre)], and low free testosterone [<5 ng/dl (0.17 nmol/litre)] among men less than age 50 yr and age 50+yr. Positive symptom reports and low total and free T were more common among older men. The presence of symptoms was more strongly related to T levels in older as compared with younger men, as indicated by a greater degree of overlap between symptom presence and low total and free T among older (52.4 % with low total or free T had symptoms) compared with younger (43.1 % with low total or free T had symptoms) men. It is noteworthy that, even in men aged >50 yr, 47.6 % of men with low T levels were asymptomatic.

Consistent with a previous work from MMAS on the association between low libido and testosterone[18], the BACH's Authors also found that the majority of men with symptoms of androgen deficiency had normal T levels, and conversely, a considerable portion of men with low T were asymptomatic. It is difficult to speculate on why these men with low T levels do not exhibit symptoms, but recent data indicate that T thresholds may be symptom-specific[19] or individual-specific20, the latter potentially related to genetic differences that affect androgen sensitivity[21,22].

Regardless of the mechanism, the BACH survey authors posed the question "What are the clinical risks of missing these asymptomatic men with low testosterone levels, if any?" Perhaps the question could be viewed from another angle: "What are the clinical risks of missing symptomatic men with 'normal' testosterone levels?" In future analyses, it will be of interest to determine whether symptomatic and asymptomatic men with low testosterone levels are at differential risk of poor skeletal health, frailty, anemia, metabolic syndrome/prediabetes, diabetes, and other outcomes postulated to have an underlying androgen component.

Fig.1 (From Araujo et al. 2007)



Testosterone Replacement Therapy: Benefit and Risks

The efficacy of testosterone replacement therapy (TRT) in subjects with LOH is still under debate, and more data are needed before TRT can be widely recommended to prolong male lifespan, even in hypogonadal men.

Nonetheless, LOH in males and its treatment is a rapidly evolving area. The benefits and risks of TRT must be clearly discussed with the patient, and assessment of prostate and other risk factors considered before commencing T treatment.

Restoring T levels to within the normal range by using TRT can improve many of the effects of hypogonadism, and should, in theory, approximate the natural, endogenous production of the hormone, and maintains physiologic serum T concentrations and its active metabolites without significant side-effects or safety concerns and, more importantly, alleviates the symptoms suggestive of the hormone deficiency. Most importantly, these include beneficial effects on mood, energy levels and patients' sense of wellbeing, sexual function, lean body mass and muscle strength, erythropoiesis and bone mineral density (BMD), cognition and some benefits on cardiovascular risk factors. Testosterone is well known to help in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition. All these benefits made TRT in the United States increase substantially over the past several years, with an increase of more than 500 % in prescription sales of testosterone products since 1993.

The risks of TRT depend upon age, life circumstances, and other medical conditions.[5] There is a risk for prostate cancer and worsening symptoms of benign prostatic hypertrophy, liver toxicity and tumour, worsening symptoms of sleep apnea and congestive heart failure, gynecomastia, infertility and skin diseases. Testosterone replacement therapy is not appropriate for men who are interested in fathering a child, because exogenous testosterone will suppress the hypothalamo–pituitary–testicular axis.

There are clinical practice guidelines from the Endocrine Society for monitoring patients receiving TRT.[4,5] Testosterone level, digital rectal exam, PSA, hematocrit, BMD, lipids, and liver function tests should be checked at baseline, then the patient should be evaluated three and six months after treatment starts, and then annually, to assess whether symptoms have responded to treatment, and whether the patient is suffering from any adverse effects.

Prevalence of TRT

The number of men on TRT in various countries is difficult to estimate accurately, because moving annual turnover figures from different governmental and commercial agencies often give only the monetary value and number of packs of testosterone sold.

In the USA, which now represents about 90 % of the market for testosterone products, the treatment is becoming more widely used. The rapid expansion in the USA is largely because of rapidly growing public awareness and enthusiasm for TRT fostered by the internet, together with safer and more convenient products, as well as easier access though private physicians rather than in a state-funded system. There the market for TRT has increased from US $49 million to almost $400 million between 1997 and 2003, with the majority of prescribing being for men 40 years and older.[25]

By contrast, according to figures for Europe and the UK provided by IMS and the British Pharmaceutical Index (BPI Data), testosterone usage in Europe is generally much lower, averaging 1 % or less of men with symptoms, except in Germany where it is better recognised and more accepted.[1] In Russia, there has been a rapid reduction in life expectancy for men, which has now fallen to about 58 years because of factors such as psychosocial stress and the ravages of alcohol. This results in a rapid fall-off in the number of men over the age of 50, and a high prevalence of LOH in this group due to the same factors.[1]

In Australia a rising trend in testosterone prescribing which started in the mid-1990s was suppressed by two successive rafts of legislation.[26] Combining Australian Bureau of Statistics figures for 2006 with those of Medicare Australia for Pharmaceutical Benefit prescriptions for 2006, it is estimated that ~1.54 % of the men over 50 likely to have LOH symptoms are receiving TRT, and of those with biochemically proven AD, just over 6 % were being treated.

Unfortunately, in other emerging markets such as China and India, there is no indication of the proportion of treated patients who are receiving TRT, even though it is well-known that several multicentre trials on LOH in men have been carried on since the 1990s.

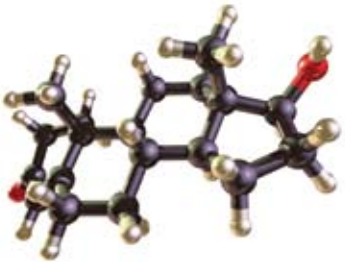
Summary

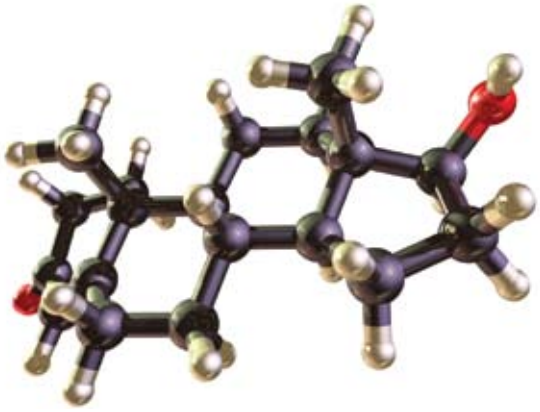
Previously, LOH has not been well understood. Studies conducted to date have been too small to address potential long-term adverse effects, and there are risks in extrapolating benefit from epidemiological studies. Many questions in the treatment of hypogonadism remain unanswered. There is a need for large clinical trials, or at least a meta-analysis of the extensive short-term data combined with analysis of long-term benefits and risks of TRT in older men with LOH.

Moreover, future clinical trials should also examine treatment patterns among men with symptomatic androgen deficiency and the profile of asymptomatic men with low testosterone levels, which might assist in understanding the mechanisms by which low testosterone levels increase risk of disease.

References

1. *Carruthers M. Time for international action on treating testosterone deficiency syndrome. The Aging Male, March 2009; 12(1): 21–28.*
2. *Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab, 2001; 86:724–31.*
3. *Feldman HA, Longcope C, Derby CA, et al. 2002. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab, 87:589–98.*
4. *Wang C, Nieschlang E, Swerdloff R, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. Consensus statement. Eur J Endocrinol 2008;159:507-14.*
5. *Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2010; 95(6):2536–2559.*
6. *Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007; 92: 4241–4247.*
7. *Gray A, Feldman HA, McKinlay JB & Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991; 73:1016–1025.*
8. *Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001; 86:724–731.*
9. *Wu FC, Tajar A, Pye SR, et al. Hypothalamic–pituitary–testicular axis disruptions in older men are differentially linked to age and modifiable risk factors. J Clin Endocrinol Metab 2008; 93:2737–2745.*
10. *Hoyert DL, Arias E, Smith BL, et al. Death: final data for 1999. National Vital Statistic report 2001;49,8.*
11. *Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008; 93: 68–75.*
12. *Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007; 116: 2694–2701.*
13. *Vermeulen A. Hormonal cut-offs of partial androgen deficiency: a survey of androgen assays. J Endocrinol Inv 2005; 28: 28–31.*
14. *Rosner W, Auchus RJ, Azziz R, et al. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society Position Statement. J Clin Endocrinol Metab 2007; 92: 405–413.*
15. *Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999; 84:3666–3672.*
16. *Hameed A, Brothwood T, Bouloux P. Delivery of testosterone replacement therapy. Curr Opin Investig Drugs 2003; 4:1213–1219.*
17. *Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in Men. J Clin Endocrinol Metab 2007; 93:4241–4247.*
18. *Travison TG, Morley JE, Araujo AB, et al. The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab 2006; 91:2509–2513.*
19. *Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006; 91:4335–4343.*





20. *Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab 2004; 89:3813–3817.*
21. *Zitzmann M, Gromoll J, Nieschlag E. The androgen receptor CAG repeat polymorphism. Andrologia 2005; 37:216.*
22. *Zitzmann M, Nieschlag E. The CAG repeat polymorphism within the androgen receptor gene and maleness. Int J Androl 2003; 26:76–83.*
23. *Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn 1997; 17:363–368.*
24. *Sijstermans K, Hack WW, Meijer RW, van der Voort-Doedens LM. The frequency of undescended testis from birth to adulthood: a review. Int J Androl 2008; 31:1–11.*
25. *Allan CA, McLachlan RI. Age-related changes in testosterone and the role of replacement therapy in older men. Clin Endocrinol (Oxf) 2004; 60:653–670.*
26. *Handelsman DJ. Trends and regional differences in testosterone prescribing in Australia, 1991–2001. Med J Aust 2004; 181:419–422.*

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Development of Melanoma Vaccine with the Help of Potato Virus

The worldwide incidence of malignant melanoma is rising at a faster rate than any other solid tumour. Although the recovery results are good in case of early diagnoses, the mortality rate for advanced stadiums is depressing. Intense research in the field of therapeutic vaccines for melanoma treatment is underway. However, none of the vaccine candidates to date have been proven effective in clinical trials.

The key to effective melanoma vaccine development may lie in interdiciplinary molecular research, where new knowledge and best practices from different areas are linked for a common goal. In Estonia a novel melanoma vaccine candidate is developed in a potato virus particle.

Worldwide Incidence of Melanoma

Internationally 132,000 new cases per year have been estimated by the World Health Organization. The incidence of melanoma depends on the geographical location, with the highest levels in Australia with a median population incidence of 34 per 100,000, and the USA with 14 per 100,000, while in Europe the levels range from five for the Mediterranean to 15 cases per 100,000 for the Scandinavian population (Lens and Dawes, 2004; Giblin and Thomas, 2007). According to the National Cancer Institute in the USA, the estimated number of new cases and deaths for 2010 is 68,130 and 8700 respectively. The mortality risk is increased with age and stage of disease. The median lifetime risk for developing melanoma in the US is 1 in 58 (Rigel et al., 2010). Fortunately the survival rates have increased remarkably over the last 30 years, with five-year survival being 93 % for the cases diagnosed in 2002. This rise is likely due to earlier diagnosis, public awareness and education on risk factors (Rigel et al., 2010). However, the survival rate is tightly associated with the stage of disease, and the survival rates for advanced disease are less than 50 %.

Mechanisms behind the Outbursts of Melanoma

Melanoma is a form of skin cancer that arises from melanocytes - the cells that produce pigment. Melanoma may begin in association with a mole. Melanocytes produce a pigment called melanin that gives the skin its colour and protects it from sun damage. Darker skin has more melanin and more protection. Melanocytes often cluster together and form moles (nevi). Most moles are benign, but some may go on to become malignant melanomas. A lot is still unknown in regard to the factors influencing the outburst and development of melanoma. Scientists are working intensively on these questions. For instance, lately a hypothesis was set according to which melanoma develops from mutated stem cells (Grichnik et al., 2006). This hypothesis needs further research.

It is evident that in the case of very early-stage diagnoses, the disease is potentially curable with surgery alone in up to 90 % of patients. However, the prognosis for patients with more advanced disease with involvment of regional lymph nodes or distant metastasis is poor, with median survival rates of 24 and six months respectively (Kim et al., 2002).

Ultraviolet rays damaging the DNA of skin's pigment cells are of cardinal importance in the development of melanoma. Thus melanoma has traditionally been a disease more widespread in areas with a high amount of annual sunshine. However, in the last decades, people from northern areas, who have not had much access to open sunshine, have developed a lifestyle full of sunbeds and vacations on sunny beaches. It seems like great fun (especially after the peak of the economic crisis), but has major drawbacks on human health.

For instance, in a small Nordic country, Estonia, oncologists estimate that melanoma incidence is increasing by 5-7 per cent per year. People aged 20-59 years are considered the age group most at risk, with the maximum risk lying with 30-year-olds.

Research in the Field of Therapeutic Vaccines for Melanoma

A vaccine could prove beneficial in cases where a person has been operated on for melanoma, but there is a risk for the return of cancer as new metastases. In people with a family history suggesting hereditary risk for melanoma, pre-emptive vaccination might be considered – if only there was such a vaccine.

Typical cancer molecular pathways are likely not involved and utilised in melanoma pathogenesis, as these tumours are radio- and chemo-resistant, and are also resistant to drug-induced apoptosis (Satyamoorthy and Herlyn, 2002). Due to limited efficacy of chemo- and radiation therapy, immunotherapy has become a major focus of investigational treatment of melanoma.

Intense research in the field of therapeutic vaccines for melanoma treatment is underway. However, none of the vaccine candidates to date have been proven effective in clinical trials. Vaccine candidates in development are intended for treatment against progression of the disease and metastasis, and not for initial prevention of melanoma. The principle of the vaccine approach is to specifically activate the organism's own immune response against the tumours, and to inhibit the tumour's protective mechanisms which it uses against the immune system. Approaches of the possible vaccines include creating vaccines from the patient's own cancer. However, as the cancer develops from the normal tissues and displays familiar properties, quite often the immune system does not recognise the difference between malignant and normal tissue, and thus problems with specificity exist. Recently tumour-specific antigens have been found which are now being tested for potential in vaccine therapy (Schmidt, 2009). Future vaccine strategies should include personalised approaches, where genetic predisposition to melanoma is evaluated and vaccinations performed only in case of increased risk of cancer development.

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Vaccination with Virus-Like Particles (VLP)

Vaccination with virus-like particles (VLP) is already in clinical use in case of hepatitis B and papilloma virus 2.

Vaccination of melanoma patients with tumour-specific antigens recognised by immune system cytotoxic T lymphocytes may produce significant tumour regressions (Kazaks et al., 2008). On the other hand, it has been demonstrated that presentation of immunogenic peptides in a highly ordered aggregate form can result in enhanced immune responses (Jennings and Bachmann, 2008; Ramqvist et al., 2008). Presentation of tumour-specific antigen(s) on specific highly immunogenic carriers such as virus-like particles (VLPs) might exert more intensive therapeutic effect. The virus-like particle technique is based on the ability of viral structural proteins to self-assemble into highly-organised symmetric structures, without the need for further viral components. Since VLPs lack viral genome, they are non-infectous. Purification of VLPs is relatively simple owing to their multimeric molecular organisation. Due to their highly repetitive structure (which means that they are relatively big), VLPs are known to induce strong antibody responses in the absence of adjuvants. Also, VLPs are able to prime cytotoxic T lymphocyte responses in vivo. After recognition, they activate the cytotoxic function of the cytotoxic T lymphocytes, leading to the destruction of tumour cells.

Melanoma Vaccine Project Initiated in Estonia

Competence Centre for Cancer Research Ltd., in collaboration with its partners Tallinn University of Technology, Kevelt Ltd. and EphaG Ltd., has started an ambitious melanoma vaccine project in Estonia. It is based on the knowledge of oncobiologists, oncologists, immunologists and plant physiologists.

The aim of the project is to work out a vaccine against human melanoma based on the ability of the human immune system to recognise bigger particles different from the ordinary antigen carriers. The idea of the project was to use plant virus A's protein particle without its genetic code as 'an empty shell'. Scientists use this empty shell like a space rocket to send useful cargo to the cancer-diseased organism: this cargo is a combination of amino acid sequences imitating the protein's characteristic to cancer found on the surface of a melanocyte transformed to cancer.

The first target was to develop an epitope presentation system based on plant virus potato A potyvirus (PVA) coat protein as a carrier of one melanoma-associated antigene. Potyvirus coat proteins can autoassemble and form virus-like particles even in the absence of the viral RNA, and they can be formed in large quantities in heterologous host expression systems (including bacterial, yeast or insect cells). We have shown that potyviral VLPs are suitable carriers to present immunogenic epitopes to the immune system (Baratova et al., 2001).

Our melanoma vaccine project is based on two important factors: knowledge about tumour-associated antigens on cancer cells and their peptides as important targets in the development of vaccines for melanoma, and a traditionally strong school of plant physiology and plant viruses in Estonia. This combination enabled us to think about plant viruses and their coat protein particles as attractive candidates for the development of peptide presentation systems.

The expected outcome of our project is pre-clinically and clinically validated

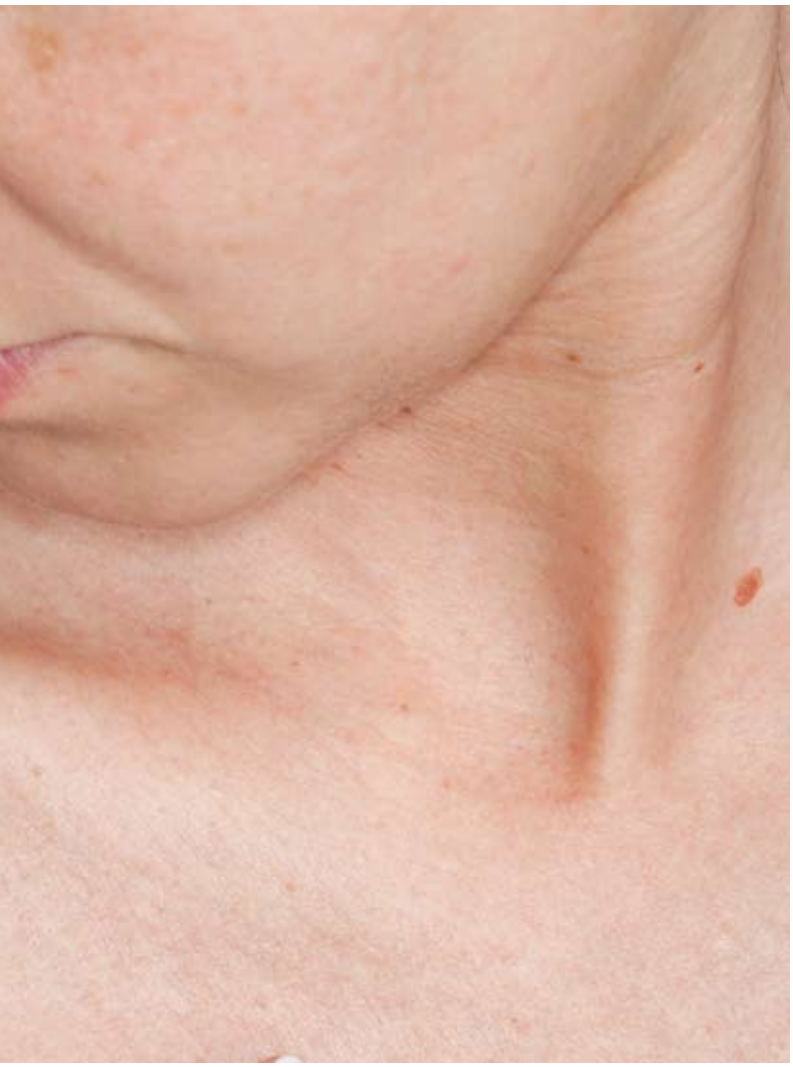
novel vaccine candidate (locally known as PVA CP VLP-mel) consisting of the melanocyte differentiation antigene encapsulated in noninfecious potato A potyvirus coat protein virus-like particle with potential immunostimulating activity. The vaccine works via strong activation of the immune system that as a result also kills the real melanoma cells (cytotoxic T lymphocyte response against cancer cells expressing the gp100 antigen resulting in tumour cell lysis).

Melanoma evolves because quite often the organism cannot detect mutated cells any more. One of the reasons why an organism is not able to detect mutated melanoma cells is the fact that pathologic melanoma cells are very similar to normal melanocytes. The main difference is in the number of certain differentiation antigenes on the cells (Sullivan, 2009).

However, any immune system is constantly on the lookout for discrepancies. Its task is to react to anything different from the ordinary. The question is whether a little mouse or an elephant is running in the blood vessels. The immune system might not notice a mouse, but it is difficult not to pay attention to an elephant (Lõhmus, 2009). Our drug candidate brings along an elephant to enable the immune system to catch the mice.

Results and Future Plans

The results of the project are promising – the vaccine candidate has worked well in mice models. Our team has shown that in most vaccinated mice the delay of the development of mela-



noma as well as which, the size was significant. In several mice, clear regression of the tumours was observed. The results are in accordance with the present knowledge of the individuality of different immune systems and with variable responses to vaccination. Thus the expected results of vaccination of humans with VLP vaccines will never be 100 %.

Future plans of the CCCR team include the optimisation of the method, introduction of new mice models and validation of the drug response in pre-clinical PET. The pre-clinical phase is expected to be finalised within a year. First phases of clinical research will be conducted together with the North Estonian Medical Centre, the biggest hospital in Estonia. New strategic partners will be searched for, either at the end of the pre-clinical phase or after the first phases of clinical research.

References

1. *Baratova LA, Efimov AV, Dobrov EN, Fedorova NV, Hunt R, Baun GA, Ksenofontov AL, Torrance L, Järvekülg L (2001). In situ spatial organization of Potato virus A coat protein subunits as assessed by tritium bombardment. J Virol 75:9696-702.*
2. *Bataille V, de Vries E (2008) Melanoma--Part 1: epidemiology, risk factors, and prevention. Bmj 337:a2249.*
3. *Giblin AV, Thomas JM (2007) Incidence, mortality and survival in cutaneous melanoma. J Plast Reconstr Aesthet Surg 60:32-40.*
4. *Grichnik JM, Burch JA, Schulteis RD, Shan S, Liu J, Darrow L, Vervaert CE, Seigler HF (2006) Melanoma, a tumour based on a mutated stem cell? J Investigative Dermatology 126:142-153.*
5. *Jennings GT, Bachman MF (2008) The coming of age of virus-like particle vaccines. Biol Chem 389:521-536.*
6. *Kazaks A, Balmaks R, Voronkova T, Ose V, Pumpens P (2008) Melanoma vaccine candidates from chimeric hepatitis B core virus-like particles carrying a tumour-associated MAGE-3 epitope. Biotechnol J 3:1429-1436.*
7. *Kim CJ, Dessureault S, Gabrilovich D, Reintgen DS, Slingluff CL Jr. (2002) Immunotherapy for melanoma. Cancer Control 9:22-30.*
8. *Lens MB, Dawes M (2004) Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. Br J Dermatol 150:179-185.*
9. *Lõhmus, A. (2009) Lahingusse nahavähi vastu elevandi, mitte hiirega. Postimees 17.09.2009*
10. *Nathanson KL Using genetics and genomics strategies to personalize therapy for cancer: focus on melanoma. Biochem Pharmacol 80:755-761.*
11. *Ramqvist T, Andreasson K, Dalianis T (2007) Vaccination, immune and gene therapy based on virus-like particles against viral infections and cancer. Expert Opin.Biol.Ther. 7:997-1007.*
12. *Rigel DS, Russak J, Friedman R (2010) The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer J Clin 60:301-316.*
13. *Satyamoorthy K, Herlyn M (2002) Cellular and molecular biology of human melanoma. Cancer Biol Ther 1:14-17.*
14. *Schmidt C (2009) Melanoma vaccines: possible progress after years of frustration? J Natl Cancer Inst 101:140-141.*
15. *Sullivan RJ, Atkins MB (2009) Molecular-targeted therapy in malignant melanoma. Expert Rev Anticancer Ther 9:567-581.*
16. *www.nccn.org, visited on 18 Oct 2010*
17. *www.vtak.ee, visited on 18 Oct 2010*

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ABPM in Clinical Trials: 3D Perspectives

Despite Ambulatory Blood Pressure Monitoring (ABPM) being used for the management of hypertension in specialist centres for over twenty years, and increasingly by GPs, its use in clinical trials remains surprisingly rare. Where it is used, it is usually as part of a sub-study rather than the primary method of measurement, where conventional blood pressure (BP) measurement with a mercury sphygmomanometer is still the predominant method used..

Conventional blood pressures measured over a clinical trial could be considered a 2D perspective on any BP changes, as it only provides a snapshot of a patient's blood pressure at one point in time. ABPM, in providing full 24-hour profiles at each visit, adds a new dimension to the data and the possibilities for analysis.

Limitations of Conventional Blood Pressure Measurement

The conventional measurement of BP by the century-old technique of Riva-Rocci/Korotkov is subject to many errors. As far back as 1964, Geoffrey Rose and his colleagues classified observer error into systematic error, terminal digit preference and bias.1,2 The phenomenon of white coat hypertension, which is induced by the observer, and the circumstances of BP measurement, introduce such random inaccuracy as to render the technique highly questionable for clinical trials.3,4 This problem remains even where mercury sphygmomanometers are replaced by automatic devices.

Current Recommendations for ABPM in Clinical Trials

The EMA (European Medicines Agency) draft revision guideline drawn up by the Committee for Medicinal Products for Human Use (CHMP) – the "Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension" – states without ambiguity that ABPM is now mandatory in all studies for the evaluation of antihypertensive drugs: "As ABPM provides a better insight to blood pressure changes during everyday activities and is better standardised than casual readings, ABPM is required for the evaluation of new antihypertensive agents".5

The primary objective of the US Food and Drug Administration (FDA) guidelines, which are still in draft form,6,7 is to obtain values for the trough-to-peak ratio, and suggest that ABPM is one method of obtaining them.

In the past, some researchers took the view that the value of ABPM is dependent on simple analyses of daytime and night-time BP, and that the technique provided a convenient method of determining peak efficacy with trough efficacy being assumed to be the value just before administration of the following day's dose. This approach fails, however, to take account of the many other analyses that can provide valuable information on antihypertensive drug effects, such as nocturnal dipping status, the morning surge, BP variability, arterial stiffness and 24-hour heart rate.

These data can be readily collected by systems, such as dabl®, to maximise the analytical yield from ABPM so as to assess as fully as possible the effects of both BP-lowering drugs and non anti-hypertensive drugs on the 24-hour profile.

What is Ambulatory Blood Pressure Measurement (ABPM)?

ABPM is a non-invasive method of measuring blood pressure readings at regular intervals, typically every 30 minutes. Subjects have a monitor fitted in an investigative site, leave, and continue to perform normal daily activities. The device is programmed to inflate and record blood pressure at specified intervals that comply with the study protocol. Modern devices are compact, lightweight and quiet, which has resulted in high patient acceptance. The subject returns to the site 24 hours later, when the device is removed and the readings validated. The monitor is connected to a computer where the 50 or so measurements are loaded for analysis and plotting. Advanced systems, such as dabl® ABPM provide automatic interpretation of the results.

Advantages of ABPM in Clinical Trials

ABPM overcomes the shortcomings of the conventional technique and provides many advantages by virtue of providing a profile of BP over the 24-hour period. Moreover, ABPM has little if any placebo effect8 and, as daytime and night-time mean pressures are less variable than CBPM, fewer subjects are required for trials that do not require drug safety data.9

A unique benefit of ABPM is the large number of parameters it provides to assess drug efficacy and safety. These parameters have the potential to indicate the mechanisms whereby new antihypertensive drugs can confer benefit, and so provide more insight into the nature of hypertension.

In addition, ABPM provides data for a number of clinically relevant analyses that can be further examined in a standardised manner to enhance the speed and accuracy of adverse event capture.

Depending on the centralised ABPM system used, these can include:

Windows of the 24-hour profile: the 24-hour period can be divided into windows, such as daytime, night-time, morning, evening, siesta and white coat (first hour). Each of these windows provides patterns of BP behaviour that may be associated with varying levels of cardiovascular risk. As the mechanisms involved in determining BP at different times differ, not surprisingly drugs can have different effects on these different windows.10,11

Circadian variation: the most important measures of circadian variation are the nocturnal dip and the morning surge.12 Nocturnal hypertension (or a non-dipping pattern) is the most important finding associated with increased target organ involvement and increased cardiovascular morbidity and mortality. Nocturnal BP is a far more stable measurement than day-

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time BP between different days. The morning surge also needs careful analysis in relation both to how it is affected by nocturnal-targeted treatment, and also, where it is steep, as a target for treatment in its own right. Circadian variation can also be analysed using hourly mean pressures. Hourly mean differences between agents provide important information on the relative efficacy of an agent over the 24 hours.

Identification of white coat responders: subjects with white coat hypertension who have elevated BP in the medical environment (and in the first hour of ABPM) but otherwise normal pressures throughout the 24-hour period can be identified and excluded from clinical trials.13 Likewise, subjects with hypertension who have higher BP measured in the clinical setting (and in the first hour of ABPM), and who might be excluded from recruitment if the clinic BP is above the entry cut-off level, can be identified and included in the study.

Mean values: measures of the levels for systolic and diastolic pressures and heart rate can be obtained for individual windows, and also for the entire 24-hour period. Mean values are most commonly used, but the further insight provided by the median, load, leese, area under the curve and percentage of high readings can also benefit from the analysis of changes to the profile.

Blood pressure variability: recent studies have shown that reducing BP variability may be as important as lowering mean BP.14–17 ABPM analysis provides not only measures of circadian variability, but also measures of short-term variability. At present, research is still needed to gain deeper insight into the causes, consequences and possible treatment of variability in blood pressure.

Derived measures: a number of indices may be derived from ABPM; the 24-hour rate-pressure product is the product of systolic pressure and heart rate, and is a measure of myocardial oxygen consumption.18 The ambulatory arterial stiffness index (AASI), which is calculated from systolic and diastolic pressure over 24 hours, independently predicts stroke and cardiovascular fatality risk.19

Assessment of drug efficacy: analysis of hourly mean BP and changes over 24 hours allow determination of the efficacy over the day, thereby showing the optimal dosing regimens for a particular drug. Traditional trough-to-peak ratio can be calculated more accurately, as well as the more recent ABPM-derived smoothness index.

Identification of drug-induced hypotension: ABPM allows ready identification of drug-induced hypotension, particularly in association with a post-prandial fall in BP and during a siesta dip - phenomena that are particularly common in the elderly.20

ABPM as a Biomarker in Clinical Trials

ABPM is important, not only in clinical trials for antihypertensive agents, but also as a biomarker for cardiovascular safety in a much broader range of clinical trials.

Biomarkers are crucial, not only to the development of safe and effective drugs, but also for determining which of similar treatments is most suitable for a particular patient. The efficacy of all drug treatment varies throughout the day, and is different for different individuals. Biomarkers for cardiovascular safety and changes are central to most new treatments. Important to the analysis are changes to the nocturnal dip and morning surge. BP variability and level may change not only in response to the agent, but also in response to another adverse effect. These responses will generally occur sometime after administration.

Cardiac safety concerns are a leading cause for the recall of marketed drugs and abandonment of drug development programmes for any indication.

ABPM provides a relatively convenient method of gathering data which, along with other biomarkers, provides data on safety or suitability. Centralised ABPM services such as dabl® can also be configured to enhance adherence to the study protocol by automatically taking measurements at time points that correlate to dose administration and other significant events.

24-hour ABPM provides a basis for several statistics which provide a valuable and comprehensive cardiovascular profile. In the context of multisite studies in emerging markets, ABPM does not require highly sophisticated equipment or trained staff, as it is a relatively straightforward and simple procedure to carry out.

Conclusion

Conventional blood pressures measured over a clinical trial give a 2D perspective on any BP changes. ABPM, in providing full 24-hour profiles at each visit, adds a new dimension to the data and the possibilities for analysis. While this has been appreciated for two decades in the management of hypertension, this has not been the case in clinical trials. There is growing acceptance that ABPM's central importance is not only in providing a facility to provide new measures of antihypertensive drug efficacy, but also as a critical tool for safety and applicability biomarkers for any drug with a potential cardiovascular effect.

In the Next Issue

One of the perceived difficulties in using ABPM in clinical trials is the logistics involved in carrying out such a trial. However, with the aid of modern software, this has become simpler, more accurate and more cost-effective than the use of conventional measurement.

References

1. *Beevers G, Lip GHY, O'Brien E. ABC of Hypertension. Part II. Conventional sphygmomanometry: Technique of auscultatory blood pressure measurement. BMJ 2001;322:1043-1047*
2. *O'Brien E. Ambulatory blood pressure measurement is indispensable to good clinical practice. J Hypertens 2003;21(Suppl 2):S11-S18*
3. *Owens P, Atkins N, O'Brien E. Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. Hypertension 1999;34:267–272*
4. *Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of Ambulatory Over Clinic Blood Pressure Measurement in Predicting Mortality: The Dublin Outcome Study Hypertension 2005;46(1):156-161*
5. *European Medical Agency, Committee for Medicinal Products for Human Use. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension. CPMP/EWP/238/95 Rev. 3 (Draft). 2009. Available from URL: http://www.ema.europa.eu/pdfs/human/ewp/023895endraft.pdf (Accessed 06 January 2010)*
6. *US Food and Drug Administration, International Conference on Harmonization (ICH). Draft Guidance: E12A Principles for Clinical Evaluation of New Antihypertensive Drugs. 2000. Available from URLs: http://www.fda.gov/RegulatoryInformation/Guidances/ucm129461.htm and http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129462.pdf (Accessed 06 January 2010)*
7. *US Food and Drug Administration, International Conference on Harmonization (ICH). Guidance on Statistical Principles for Clinical Trials; Availability. Federal Register 1998;63(179):49583-98. Available from URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129505.pdf (Accessed 06 January 2010)*
8. *White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. Am J Hypertens. 1999;12(2 Pt 2):50S-55S.*
9. *Dolan E, Thijs L, Li Y, Atkins N, McCormack P, McClory S, O'Brien E, Staessen JA, Stanton AV. Ambulatory Arterial Stiffness Index as a Predictor of Cardiovascular Mortality in the Dublin Outcome Study. Hypertension 2006;47(3):365-370*
10. *Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G. The smoothness index: a new, reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension. J Hypertens. 1998;16(11):1685-91*
11. *O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P with the statistical assistance of Atkins N and Gerin W on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. International protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3-17*
12. *Stanton A, Cox J, Atkins N, O'Malley K and O'Brien E. Cumulative sums in quantifying circadian blood pressure patterns. Hypertension 1992;19:93–101*
13. *O'Brien E, Atkins N, , Stergiou G, Parati G, Asmar R, Imai Y, Wang J, Mengden T, Shennan A on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. European Society of Hypertension International Protocol for the Validation of Blood Pressure Measuring Devices in Adults. 2010 Revision. Blood Press Monit 2010;15:23–38*
14. *Stergiou G, Karpettas N, Atkins N, O'Brien E. European Society of Hypertension International Protocol for the validation of blood pressure monitors: A critical review of its application and rationale for revision. Blood Press Monit 2010;15:39–48*
15. *O'Brien E, Atkins N. Can improved software facilitate the wider use of ambulatory blood pressure measurement in clinical practice? Blood Press Monit 2004;9:237–241*
16. *O'Brien E. Ambulatory Blood Pressure Measurement: A Trove of Hidden Gems? Hypertension 2006;48;364-365*
17. *McGowan N, Atkins N, O'Brien E, Padfield P. Computerised reporting improves the clinical use of ambulatory blood pressure measurement. Blood Press Monit 2010. In press*
18. *Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to- visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010; 375: 895–905*
19. *Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS on behalf of the ASCOT-BPLA and MRC Trial Investigators Effects of blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurology. www.thelancet.com/neurology Published online March 12, 2010 DOI:10.1016/S1474-4422(10)70066-1 1*
20. *O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P with the statistical assistance of Atkins N and Gerin W on behalf of the Working Group on Blood Pressure Monitoring of the European Society of Hypertension. International protocol for validation of blood pressure measuring devices in adults. Blood Press Monit 2002;7:3-17*

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Understanding User Preferences for Interactive Voice and Web Response Systems in Global Clinical Trials

PEER REVIEWED

As industry-sponsored clinical trials become more global in nature, biopharmaceutical companies are increasingly using Interactive Voice and Web Response Systems (IVRS/IWRS) to manage patients and drug supplies internationally. This trend will proliferate, as recent data indicates that trials will continue to shift from the United States and Western Europe to emerging regions in order to overcome challenges relating to recruiting patients, improving research and development (R&D) productivity, and gaining regulatory approval for new drug applications.

There is a revolution happening in the conduct of clinical trials. Faced with challenges relating to R&D productivity, biopharmaceutical companies are increasingly turning to emerging regions and technology solutions to improve the efficiency of clinical trials. While the typical clinical trial of 1985 would likely have been conducted mainly in North America and Western Europe, today there is a clear shift of trial activities to emerging areas in Central and Eastern Europe, Asia, Latin America, and Africa.

Several factors are driving the internationalisation of clinical trials. Commercially, sales of pharmaceuticals in 2009 grew at 3-5 % in Europe and the United States, compared to 13-15 % in Asia, Africa, and Australia, and 10.6 % in Latin America. Moreover, IMS has forecasted sales growth of 3-6 % for United States and Western Europe, and 12-15 % for Latin America, Asia, Africa, and Australia annually through 2014.[1] With sales growth shifting to emerging areas, biopharmaceutical firms deem it prudent to conduct trials in those regions.

Operationally, sponsors are being challenged to improve R&D productivity and trim trial costs. One of the keys to achieving those objectives is to more successfully recruit and retain patients for clinical trials.[2] As sponsor companies have seen their demand for clinical trial participants grow from 2.8 to 19.8 million in recent years, and have witnessed a rapid decline in the participation of patients in Western nations (and hence increased study delays), they have turned to emerging areas as a solution to recruiting patients. Recent data indicates that this strategy is helping solve the patient recruitment challenge – sites in emerging nations are enrolling more patients per site than their Western counterparts.[3]

Meanwhile, biopharmaceutical companies are adopting clinical technologies as a means to improve R&D productivity. Today, study sponsors are executing complex global study designs and protocols efficiently through the use of a wide range of technologies to collect safety and efficacy data for regulatory submissions. Innovative R&D methodologies involving translational medicine, adaptive designs, and the "learn and confirm" paradigm, all require access to real-time data to make decisions during trials. Hence, clinical trial practitioners are incorporating a range of e-technologies into clinical trials, including Interactive Voice and Web Response Systems.[4]

Industry sponsors commonly use IVR/IWR in global clinical trials for a variety of purposes that can be grouped into two main categories: patient management, and drug supply management. In terms of the former, clinicians use IVR/IWR systems to recruit, screen, and enroll patients into a clinical trial. Once a patient is enrolled into the trial, clinical trial site personnel use IVR/IWR to randomise and assign the investigational drug to the patient in a blinded manner. Thereafter, study professionals manage subjects' visit schedules and collect trial data through the use of IVR/IWR systems. Moreover, in trials involving patient reported outcomes, clinicians apply IVR/IWR to collect data directly from patients that is eventually used to support regulatory submissions, label claims, and other product interests.[5]

Advanced practitioners also take advantage of sophisticated functionality built into many IVR/IWR systems, including the technology's ability to calculate and administer complex dose titration schemes. For example, clinicians occasionally find it necessary to use shamming algorithms on laboratory values to protect the blind in studies involving certain therapeutic areas. When those statistical needs arise, they are executed through the use of IVR/IWR functionality. Finally, with adaptive designs becoming more prominent, sponsors are making changes during the course of trials (e.g., adjusting doses or treatments arms) using advanced transactional functionalities provided by IVR/IWR systems.[6]

The use of IVR/IWR for drug supply management during a clinical trial is equally important. Clinicians and drug supply managers rely upon IVR/IWR systems for a variety of purposes, including managing drug inventories, expiration dates, and temperature excursion data, as well as ordering and tracking shipments of supplies globally. In global trials that involve a number of main, regional, and local depots, as well as multiple clinical trial sites, IVR/IWR technology provides the most cost-effective solution available to study sponsors for efficiently managing drug supply. This is particularly true for trials on biological products, which are often very expensive and require advanced monitoring and special handling to avoid waste.

There are a variety of challenges that clinical trial practitioners encounter when using IVR/IWR technology (see sidebar). This article will focus on an issue that has a ripple effect on every facet of a study: selecting the appropriate technology (IVR vs. IWR) to capture data from site practitioners and patients. The ability to mix and match technologies based upon user preferences can

Key Challenges Implementing IVR/IWR in Global Clinical Trials

- Managing multiple languages consistently across IVR and IWR systems
- Getting systems live with all functionalities given IVR/IWR is typically procured inside three months of a trial's live date
- Finding vendors with the experience, capabilities, resources, and expertise to manage global trials
- Providing technical and study-related support to sites and patients throughout a trial in native languages
- Proactively monitoring and managing drug supplies to avert shortages that lead to study delays
- Reducing duplication in data entries, and resulting errors, across e-clinical technologies and paper that may cause costly delays before data lock and statistical analysis.

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sometimes dramatically impact the quality of data collected during a trial and the subsequent strength of a regulatory submission. Making it easy for a professional on a clinical trial site or a patient to input data eases the burden of information collection during a trial. To do so, however, requires an understanding of technology users.

One of the main challenges that trial sponsors face when implementing IVR/IWR systems is gauging the preferences of site personnel and patients in terms of phone versus web. Through continued experience in global trials, leading technology service providers and industry sponsors are beginning to see trends emerge relating to user preferences between IVR and IWR technologies.

Among the most prominent trends is the preference of users to have access to both phone and web systems in concert during a clinical trial (see sidebar for an explanation of this trend). This preference is held by sites and sponsors on a global basis. However, regional differences are becoming evident. For example, sites located in Central/Eastern Europe, Asia, and Latin America prefer to use the web more frequently to manage patients than do their counterparts in Western Europe, North America, Australia, and Africa. Even within countries, particularly large nations that have diverse geographical regions and populations, there is variability in preferences for web vs. phone.

These varied preferences are tied to key infrastructural, operational, cultural, and personal-use issues at sites across the globe. Most Western European and North American sites have enjoyed advanced telephony systems for many decades. Given their experience using IVRS technology, they have been slower to adopt IWRS technology than their counterparts in emerging regions. Conversely, clinical trial sites in emerging nations, specifically in Asia and Central/Eastern Europe, have been fast to adopt IWR because of less prior experience using the phone and due to the development of advanced web-based digital systems and mobile technologies in some of those regions over the past ten years. Certain areas of Africa, by contrast, do not have comparable digital technology infrastructures, and hence prefer using the phone to manage patients. In sum, there are fine differences that sponsors must understand in order to select the appropriate technology for specific global sites.

Sponsors' preferences for technology options (i.e., phone vs. web) also vary depending upon the type of data collected, the regions in which information is generated, and the decisions that need to be made during a trial. For example, in trials that incorporate electronic patient reported outcomes (ePRO), sponsors are increasingly opting for a multi-modal approach to data collection in order to increase patient compliance, generate a robust data set, and to assure patient safety, according to a recent research study sponsored by Almac involving 98 professionals in biopharmaceutical firms.

Almac's research with sponsors reveals some interesting trends in the provision of ePRO technology for global trials. For example, when asked what factors drive their decision to select a particular technology for ePRO data collection, the top four responses given by participants were "reliability of method" (39 %), cost (38 %), "ease of use" by patients (35 %), followed by "need for rapid access to data" (33 %). Sponsors explained those responses during interviews by stating that ePRO studies often require high rates of compliance to satisfy regulatory agencies, therefore reliable technologies that facilitate compliance are strongly preferred.

Main Reasons Sponsors Prefer Access to both IVR and IWR for Global Trials

- The need for a backup method in case either the phone or the web is not available at any given time
- Varying levels of access to technologies at clinical trial sites worldwide
- Different preferences for phone vs. web amongst users depending upon their location, past experience, level of technical proficiency, and tasks to be completed
- Ability of sites and patients to enter and/or access data no matter the location (i.e., while away from the trial

Sponsors also explained that some of their ePRO studies measure the effects that particular medicines have on a patient's quality of life, including adverse effects. Therefore, having rapid access to data helps sponsors ensure patient safety throughout the trial.

Given the need for technologies that are reliable, but also cost-effective, sponsors indicate that IWR is quickly becoming the technology of choice for use in ePRO studies. When asked which technologies they use today and those they will use three years from now, sponsors indicated that the two fastest-growing methods are IWR/web (today 32 %, increasing to 49 % in three years) and mobile internet (11 % today, growing to 32 % in three years). By contrast, the most popular method today (paper) will decrease in use from 43 % of trials today to 21 % in three years. The second most popular method, handheld devices, will remain a viable option, but will grow at a slower rate than IWR and mobile internet.

While the web will continue to grow in importance as a means to collect data from sites and patients, sponsors reveal that future clinical trials will require the use of multiple modalities to efficiently collect data. When queried as to their likelihood to use more than one device/method in combination in a given trial involving ePRO, 81 % of sponsors stated that they currently use multiple methods today, or are "very likely" or "somewhat likely" to do so in the near future. Only 19 % of sponsors indicated that it was "possible but not very likely" or "it is not likely at all" that they will use multiple modalities (e.g., phone, web, handheld devices) for patient reported outcomes data collection.

In conclusion, given the challenges of conducting trials on a global basis, industry sponsors of clinical studies are rapidly adopting IVR/IWR technologies to more efficiently manage patients and drug supplies. A variety of technical, infrastructural, cultural, and user preference-related factors are driving sponsors to seek flexibility in technology choices for global trials. Hence, they are seeking multi-modal approaches to technology provision that involve both phone and web-based applications to assure that trials run efficiently. Such technologies facilitate complex designs and sophisticated R&D methodologies, such as adaptive trials and translational medicine, because they provide flexibility in data collection for users, control costs, and provide rapid access to data for sponsors.

Joseph Bedford, Ph.D. is a Director at the Almac Group, where he is responsible mainly for strategy, marketing, and product management matters in the Clinical Technologies business unit. Prior to joining Almac, Dr. Bedford spent six years at Covance, where he held positions of Associate Director of Global Market Research and Director of Marketing and Strategy. Dr. Bedford has published several articles and spoken at industry conferences on topics such as biopharmaceutical drug development, R&D outsourcing, clinical technologies, and corporate strategy.

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- Be updated on the latest developments in the use of *in vitro* assays to replace *in vivo* studies, with guidance from the **Health Protection Agency. University of Milan** and **GlaxoSmithKline**
- Overcome the challenges of filing technical variations both in the US and Europe, with expert advice from **Dr Andrew Deavin** from **GlaxoSmithKline**
- Advancing characterisation of adjuvants: Hear the latest work from the **Statens Serum Institute** and the **Bill and Melinda Gates foundation**

Conference 2

Vaccine Scale-Up and Manufacturing

- Hear from **Dr Robert Repetto** of **Pfizer** on the application of Quality by Design principles to manufacturing with single-use systems processes
- **Dr Mark Thompson** from **MedImmune** presents an update on the scale up process for their attenuated Respiratory Syncytial Virus (RSV) vaccine, exploring how they optimised their production facilities
- Be updated on the latest delivery systems and manufacturing technologies from the **Fraunhofer Centre for Molecular Biotechnology** and **Intercell**
- Learn from **Pfizer's** experiences in scaling up purification columns whilst maintaining binding capacity, with a presentation from **Dr Ning Li**

Conference 3

Vaccine Business Strategy

New Stream for 2010

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Reviewing the progress made in the development of malaria vaccine candidates and exploring the MVI strategy

Dr Christian Loucq, *Director,* Malaria Vaccine Initiative, PATH, USA

Modern Vaccines – How Business has Changed over 20 Years

Michel Baijot, *Vice President Business Development & Strategic Alliances,* GSK, Belgium

KEYNOTE SPEAKERS:

Applying QbD for vaccines production with single uses system processes

Dr Robert Repetto, *Director of Strategy and External Affairs,* Pfizer, USA

Biophysics in adjuvanted vaccine formulations: The weakest link in modern vaccine development?

Dr Geert van den Bossche, *Senior Program Officer,* Bill and Melinda Gates Foundation, USA

Big Pharma viewpoint - Collaborating in an evolving cancer vaccine field

Dr Joyce Pei, *Director, Global Business Development,* Roche Pharma Partnering, USA

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Do You Really Know what Electronic Data Capture (EDC) can Bring to You?

PEER REVIEWED

During the setup phase of clinical trials, registries, observational studies or surveys, decision-makers are mostly unaware of the true added values provided by Electronic Data Capture (EDC). This is why we would like to go "back to basics", highlighting in this paper how EDC can help all stakeholders involved in such studies.

In a recent past, the collection of clinical information was exclusively a manual process: patient data were collected on paper Case Report Forms (CRFs). Data were then double-entered into a statistical software. After the double data entry phase, when inconsistencies were detected, the CRFs needed to be checked, updated and signed off manually. It was a time-consuming and very expensive process. The risk of error was dramatically high, and audits by health authorities were real nightmares.

To speed up the clinical development process, the results of studies have to be delivered in the most rapid and efficient way possible. By capturing and monitoring data electronically and by storing them in an advanced database, clinicians, data managers, biostatisticians and monitors can work together using a single, centrally-managed global database, regardless of their geographic location and/or language.

Today, companies from the pharmaceutical, biological and biotechnological sectors, including the medical device sector, have widely adopted EDC solutions, since they offer remarkable advantages that increase the probability of clinical trial success.

EDC enables more efficient studies, improves data quality and speeds up the decision-making process. At any time the clinical development manager can with a simple mouse click know everything about enrolment (overall and in each centre), follow-up (each visit) and completion rates. There is no more need to wait for the visit of the clinical research associate (CRA) to the investigational centre to obtain this pivotal information.

Did You Say eCRF?

The term eCRF stands for Electronic Case Report Form. Basically a CRF is a paper questionnaire used in clinical trials. The CRF is used by investigators, study nurses, project coordinators, CRAs (clinical monitors) and data managers to collect, review and organise data from each investigational site. The CRF can be limited to one single handwritten page, but can also grow to a thousand-page document. With electronically captured data gathered over a period of weeks or months, eCRF allows data to be centralised, organised and accessible within a global electronic platform known as an "e-Platform" or "Web Portal".

Why Should You Use eCRF?

Rely upon eCRF to organise your clinical studies, developing biological or medical knowledge. With eCRF, data collection and reviewing steps are improved by detecting and flagging inconsistencies in the monitored data, enabling the generation and follow-up of queries online. The overall clinical trial process is implemented in a secure and centralised system with a permanent audit trail. Patient data collected by a panel of investigators are captured, authenticated, monitored and integrated in a database for easier statistical analysis.

The Bright Side of EDC

The cost of clinical development, and at the same time the requirements of health authorities, have never been so high. The upper management of pharmaceutical companies are therefore confronted with the necessity to take rapid and efficient decisions. Consequently, maximum pressure is put on clinical development teams to deliver high-quality outputs within the shortest delays possible. With EDC technology, the cost of operations is better controlled; time is saved, and therefore also money. The quality of the data is dramatically improved. Companies, research organisations, investigators and agencies can better assess the progress of a study. This gives them insight into each conducted study.

EDC helps in simplifying and accelerating the study process. It provides unsurpassed flexibility to cope with mid-study changes and to protect study data from unintended views or alterations. With an evolved architecture, eCRF integrates cross-fields, cross-forms, cross-visits edit checks, validation controls and even score calculations.

EDC = Data Security.

The use of EDC in clinical trials has a lot more aspects to be considered beforehand than when you plan a paper-based project. If you plan to use EDC, make sure you have evaluated factors such as centralisation, access, data monitoring, integration in a given environment, deployment and security. Every clinical trial needs to be deployed in a professional environment, ensuring database hosting under optimal conditions of security, confidentiality and accessibility.

eCRF for Investigators

eCRF helps investigators include their patients, and when required, allocate them to the right randomisation arm generated automatically by the database. Every investigator is allowed to follow the status of each patient online. Furthermore the quality of the data can be checked at the time of data capture. Each investigator has the right to manage their study process to check its evolution daily, and modify the information if needed. Access is provided to the full audit trail history of modifications for improved follow-up of patient data.

Eclinical Trials on the CRA Side

CRAs include any person involved in monitoring clinical trials. These fundamental actors of study quality are directly concerned by the benefits of electronic clinical trials (Eclinical tri-

als). Collection and organisation of medical records through a secured EDC environment help CRAs to navigate through data and check if electronic medical records are consistent. Progress notes can be directly added to the system by different stakeholders (doctors, study nurses, etc.) at the same time. This ensures that CRAs are always up to date and able to access quality data for further analysis.

How can EDC help Randomise Patients?

Randomisation is the process of assigning clinical trial participants to treatment groups. It gives each participant a pre-defined chance of being assigned to any of the groups. Successful randomisation requires that group assignments cannot be predicted in advance. The process of randomisation aims to ensure similar levels of all risk factors in each group; not only known, but also unknown. Characteristics are rendered comparable, resulting in similar numbers or levels of outcomes in each group.

The traditional way of doing randomisation in clinical trials was through sealed envelopes. Today, Interactive Web Response Systems (IWRS) provide centralised randomisation integrated with EDC into one system, and make it easy for handling complex randomisation schedules with multiple layers of stratification and dynamic allocation.

However, the utility of IWRS is not limited to randomisation, it allows for much more: email/fax confirmation of treatment allocation, interaction between IWRS and e-Platform, drug supply management, access to profile-dependent online reports, etc…

How EDC helps with Adverse Events Management

Conventional management of (serious) adverse events (S/AE) using a full paper process has been optimised with the use of EDC and Electronic Data Management solutions, without interfering with sponsors' standard operating procedures. There are some workflow solutions available allowing efficient AE/SAE tracking, follow-up, monitoring, coding and reporting:

- AE/SAE forms easily accessed through the user interface
- Chaining of AE/SAE forms with eCRF pages as soon as an event is recorded
- Automatic email/fax notification to the drug safety officer
- Restricted access to the drug safety officer for review of patient information
- AE/SAE Medical Dictionary for Regulatory Affairs (MedDRA) coding through the e-Platform (directly in eCRF pages or via upload)
- Access to comprehensive online reports for easier tracking and overview.

What about the Management of Quality of Life Data?

More and more frequently, clinical trials, post-marketing surveillance projects and registries are focused on the collection of quality of life (QoL) data that need to be provided by patients either during the site visit or at home. The usual way to collect QoL data is to provide patients with paper questionnaires (often scales) that need to be encoded by a trusted third-party before analysis. However there are some other alternatives to increase data processing speed and improve the interaction with physicians' data, allowing for comprehensive online data management, reporting and monitoring:

- QoL in eCRF: study site personnel retype QoL content in 100 % similar eCRF pages
- Scanning QoL paper forms: we collect, process, validate and monitor QoL paper forms
- QoL forms completed on user-friendly electronic diaries, i.e. patients use provided handheld devices based on mobile data export.

Conclusion

Integrated e-Platforms supported by EDC allow the best involvement of all clinical trial stakeholders for state-of-the-art management of Phase II-IV clinical trials.

Is this reality? Yes, it is! Authorised users have access to a single point-of-entry where they reach tools specifically designed for them. From a single, centrally-managed global e-Platform, here is a snapshot of the tools which add the most value according to user profiles:

- Physicians / study nurses: access an intuitive eCRF designed according to the most stringent data validation plans, randomise patients (any stratification), access a personalised printable calendar of visits to be handed over to the patient, view built-in study flow, reach all relevant study information, view inconsistencies for correction, reply to queries, report (serious) adverse events easily, are prompted in a timely manner of the next patient visits and of clinical re-supply, etc…
- CRAs / data managers: access data (read-only) tightly linked to a comprehensive audit trail, view customised online status reports, view inconsistencies, manage queries, manage patient sign-offs with physicians (resulting from optimised interaction between CRAs and data managers), are prompted of any relevant information, etc…
- Project managers: access comprehensive status reports, download the study database, give their 'green light' before order confirmations are sent to the warehouse, reach e-Administration tools for further reporting of CRA activities and sites management.
- Sponsor: follows-up on comprehensive study status, including site activities and management.
- Patients: access a dedicated section of the e-Platform for online completion of diary or quality of life data.

E-Platforms also allow for optimised interaction with central labs, the warehouse, or any kind of external data sources (randomisation by phone, electronic patient reported outcome (ePRO) devices, imaging, etc…).

Christophe Golenvaux, Director of Sales and Marketing at Lambda-Plus, is a strong defender of intuitive electronic data capture and electronic data management solutions. He has over 10 years' experience in the promotion and support of user-friendly and cost-effective EDC solutions. Over the last decade he has spent most of his energy in the promotion of e-Platforms that meet each study-specific requirement. He has developed an international network of small, mid-sized and large CROs that share his vision.
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An Interview with James Haughwout of CMED Technology about Timaeus 5 and Timaeus HotSpot

Question: Who is Cmed Technology, and what is its focus?
Answer: Cmed Technology, an eClinical technology provider, offers a single platform for electronic trial design, electronic data capture (EDC), medical coding, data management (for electronic, paper and hybrid trials) and real-time reporting. Its Timaeus unified eClinical platform has been built to respond on-demand to the needs of investigators, data managers and study teams.
Timaeus' unique architecture uses advanced distributed cloud computing and mobile technologies to provide the freedom to manage any type of data, for any protocol, anywhere. Timaeus has been used in every phase of clinical research — including early phase, pivotal and late phase studies as well as in globally established and emerging markets — covering single-unit clinics to multi-thousand-person studies across Europe, Asia, Africa and the Americas.

How long have Cmed Technology and Timaeus been in the eClinical industry?
Answer: Cmed Technology has its roots in the University of Oxford, starting in 2000 as ThirdPhase Ltd. After acquisition by Cmed Group Ltd. in 2002, it became Cmed Group's technology research and development division, where it developed and proved its on-demand eClinical capabilities from within Cmed Group's operational contract research organisation (CRO). In May 2010, Cmed Group commercially launched Cmed Technology to provide Timaeus directly to study sponsors, functional service providers and CROs, and to more easily partner with systems integrators, consultancies and technology providers. Timaeus has been in use since 2003.

How is Cmed Technology different from other eClinical providers?
Answer: Early on, Cmed Technology realised that legacy eClinical architectures presented too many constraints to support 21st century clinical trials. Their centralised databases easily became a performance choke-point, and served as single points of global system failure. Their reliance solely on internet browsing forced all users — including sponsors, data managers, monitors and clinicians — to have dedicated, high-speed internet connections — a condition that is often not met in the real world.
As a result, Cmed Technology took a different approach, bringing together virtualisation, content management, publishing, web, appliance and mobile technologies into a leading-edge distributed architecture, resembling the world's largest, most reliable information systems, rather than legacy eClinical ones. With Timaeus, clinicians can work over the internet, mobile and satellite connections. They also have full access to eClinical data and functionality offline when none of these are available, due to bandwidth or connectivity issues.
Because of Timaeus' forward-looking architecture, Cmed Technology is able to harness new innovation as it occurs — without large effort or investment. Cmed Technology first did this in 2004 while conducting clinical trials entirely over mobile phone connections, enabling operation in markets where mobile data technology was "leapfrogging" fixed-line technology. Later, in 2007, it quickly leveraged its abstract data architecture to enable CDISC import and export of both transactional data and metadata. In 2009, it integrated trial simulation technology into its native adaptive trial design and execution capabilities. Now, in 2010, it has added the "plug-and-play" ability to support tablet computing, expanding the range of interface technologies available to doctors, nurses and monitors.

How does the Timaeus eClinical platform help research organisations respond on-demand to the needs of studies during study startup, conduct and closeout?
Customers of Timaeus can respond on-demand to clinical trials needs in a fully validated manner from start to finish:
- Study startup:
  - o Configure the entire trial (page definitions and validation checks for capture, coding, management reporting, etc.) from a single point. Do this with equal agility for simple and complex protocols alike. Support challenges like adaptive trials and rapid proofs-of-concept (POCs) "out-of-the-box".
  - o Provision capacity for new studies, sites and users without adding, integrating and validating new hardware and systems infrastructure.
  - o Operate globally wherever investigators, monitors and patients are. Electronically capture and automatically check data at the source — online or offline — using PCs, tablets or mobile appliances. Reduce operating costs by eliminating the need for dedicated high-speed internet connections.
- Conduct:
  - o Go live incrementally — at the push of a button — as pages and validation checks are approved for release.
  - o Perform systems maintenance without downtime, eliminating frustrating outages. Execute protocol amendments worldwide without interrupting site operation.
  - o Empower investigators, monitors and data managers to capture and clean data more efficiently by enabling them to work globally from the same set of data, at the same point in time.
  - o Enable research organisations to detect and respond to problems sooner, using real-time reporting.
- Closeout:
  - o Increase capacity to support database loading by enabling servers "in the cloud" to be easily added during peak times, and accommodating the number of clinicians verifying their queries before they move to analysis.
  - o Scale capacity as demand increases, ensuring consistently fast operation through all stages of the study, for all users worldwide.
  - o Use ad hoc reporting for accurate insight to make more informed recommendations.

Last month Cmed Technology previewed two new products simultaneously at two industry conferences: SCDM (Society for Clinical Data Management) in Minneapolis, MN, and PhUSE (Pharmaceutical Users Software Exchange) in Berlin, Germany. What are the products?

Answer: Timaeus 5 — Cmed Technology's newest version of its unified eClinical platform to manage data from study design through reporting — adds enhanced usability, extended operational capabilities, streamlined investigator and monitor interaction, and expanded reporting capabilities.

Timaeus HotSpot is the industry's first portable, regulatory-compliant fully-functional eClinical suite that allows research organisations to set up clinics more easily, and provide physicians with fast, reliable access to clinical trial data using a standard Windows® notebook PC, Apple iPad® or other mobile appliance. It's just as simple as connecting to the internet via a WiFi hotspot at the airport or coffee-house, without any additional network cabling.

What are some of Timaeus 5's new advances that benefit investigators, monitors, data managers and study teams?

Ease of use: Improved usability to simplify: data access; data entry; resolution of upfront validation errors; and response to manual queries.

- Flexibility: Integration of dynamic forms with Timaeus' native adaptive trial functionality to support mid-study changes and unscheduled visits in an intuitive, efficient manner.
- Freedom: Extended operational capabilities that allow study teams to choose from an expanded range of internet browsers, and mobile and portable computing appliances.
- Efficiency: Streamlined interaction between investigators and monitors to improve efficiency and clarity of targeted source data verification (SDV) — on site and during remote monitoring.
- Insight: Expansion of Timaeus' built-in reporting through addition of clinical business intelligence capabilities and live streaming of data into life sciences hubs and analytics systems.

How has Timaeus HotSpot helped clinical trial sites become more autonomous?

Timaeus HotSpot empowers research organisations and study teams to operate more efficiently, in more places, with more freedom and flexibility. It extends an autonomous "piece" of the Timaeus cloud inside the clinic using a dedicated, secure eClinical hub.

First and foremost, Timaeus HotSpot ensures fast operation at all times — even during the business periods of clinical trials (such as during database lock).

Second, it ensures "always-on" access to eClinical data and functionality. Physicians and nurses can continue to work even if the internet connection between the clinic and the organisation managing the trial is interrupted. (Clinic staff will not even have to worry about this: Timaeus will automatically synchronise all data updates in the background when connectivity is re-established, just like your smartphone synchronises when you get off an aeroplane.)

Additionally, research organisations managing trials can provision clinics quickly and at lower cost. They do not have to manage provision of a high-speed internet connection (or open clinic firewalls). Timaeus HotSpot provides a secure, private connection from anywhere that has access to electrical power and a GSM mobile connection.

James Haughwout is Vice President of Commercialisation and Operations for Timaeus, a unified distributed eClinical platform that has been built to respond on-demand to the needs of investigators, data managers and study teams. Over the past 17 years, James has produced software and information systems used globally by more than 130 million people and 400 enterprises. In addition, he combines business process reengineering with advanced technologies within the biopharma industry to transform capabilities in clinical data and submissions management.

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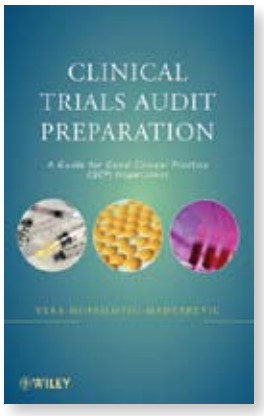
Clinical Trials Audit Preparation
A Guide for Good Clinical Practice (GCP) Inspections



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

The relevance and importance of the regulatory environment for new drug development cannot be over¬emphasised. Regulatory affairs professionals at biopharmaceutical companies keep in constant dialogue with regulatory agencies throughout development, and their input to study teams and executive management is critical throughout the process. Regulatory agencies conduct various audits during the development and manufacture of biopharmaceutical drugs. One of these is the good clinical practice audit. This book provides an excellent introduction to this topic, and a roadmap for successfully navigating such audits.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has several goals. As noted on its web site (www.ich.org), it makes recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for drug registration (approval) across different geographical regions to reduce (and ideally obviate) the need to duplicate the testing carried out during the research and development of new medicines. The intent is to permit a more economical use of animal, human, and material resources without compromising safety. ICH encourages the implementation and integration of common standards of documentation and submission of regulatory applications by disseminating harmonised guidelines. Of particular relevance here is the 1996 ICH Guideline E6(R1), "Guideline for Good Clinical Practice".

Good clinical practice (GCP) is one of three areas in which ICH has provided guidance, the others being good manufacturing practice (GMP) and good laboratory practice (GLP, pertinent to nonclinical research). As stated in ICH E6(R1), GCP is "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible." At the time the guideline was being developed (mid-1990s) the major pharmaceutical markets were the European Union (EU), Japan, and the United States (US), and so harmonisation amongst their regulatory agencies is explicitly mentioned as a primary goal. However, the guideline also mentions Australia, Canada, and the Nordic countries. Additionally, regions of major clinical trial activity, and pharmaceutical demand, have increased dramatically since the guideline's release: examples include Africa, Central and Eastern Europe, the Middle East, India, China, and Latin America. While individual regulatory agencies differ in the details of their procedures, compliance with the spirit of GCP is therefore now a worldwide concern. This book is therefore relevant to a worldwide audience.

Clinical Trials Audit Preparation addresses a wide range of relevant topics, including: the roles of the biopharmaceutical sponsor of a clinical investigation, the institutional review board (IRB) or independent ethics committee (IEC); the roles and responsibilities of the clinical trial investigator; preparing for an audit/inspection; the audit report and Form 483; warning letters issued to investigators and sponsors, and their potential influence on the new drug development process; and fraud and misconduct in clinical research (this is rare, but unfortunately does exist). As the author notes, "GCP inspections of clinical trial sites are the challenges that clinical research faces in demonstrating data credibility and patient safety." Preparation for an inspection is a laborious process, and some would say a tedious process too. The author is well aware that the topic of GCP compliance can seem "dry," and therefore takes care to utilise examples as much as possible to illustrate the complexities and demands of the process. Both internal sponsor audits and inspections by regulatory agencies are vital to ensure compliance with the sponsor's own standard operating procedures, GCP, and formal regulatory requirements.

To help the reader, in addition to the detailed and meticulous discussions in the book's five chapters, appendices provide ready access to fundamental literature. Following Appendix A, which provides answers to particularly problematic questions, the following documents are provided: ICH E6; The World Medical Association Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects; The Nuremberg Code; and the Belmont Report. Having these reports handy when reading the text of the book will prove very useful to readers.

Clinical Trials Audit Preparation is recommended to readers, and receives the JCS Library Award.

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Reviewed by: *J Rick Turner, PHD Editor-in-Chief –* ***JCS Book Review Corner****. He is Senior Scientific Director, Cardiac Safety Services at Quintiles, and also an accomplished author and editor who has a real passion for books.*

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PAREXEL COMPLETES 200 PATIENT STUDIES IN ITS EARLY PHASE UNITS OVER THREE YEARS

Assists Biopharmaceutical Companies in Making Earlier "Go/No-Go" Development Decisions

Boston, MA, November 17, 2010 — PAREXEL International Corporation (NASDAQ: PRXL), a leading global biopharmaceutical services provider, today announced that it reached a milestone of completing 200 early phase studies in patient populations during the past three years. The studies, which were conducted in-house by its early phase units worldwide, enrolled more than 3,000 patients. Early phase studies conducted in targeted patient populations are designed to demonstrate early signals of safety and efficacy in investigational medicines.

"To avoid costly late stage development failures, the biopharmaceutical industry has placed increased emphasis on conducting more complex, sophisticated, and rigorous early phase research, including earlier patient studies, to better predict safety and efficacy as well as identify and select the most promising new compounds. To assist clients in achieving these goals, PAREXEL provides access to numerous patient populations for early phase studies, including Proof-of-Concept studies," said Sy Pretorius, M.D., M.S., M.B.A., Corporate Vice President and Worldwide Head of Early Phase, PAREXEL. "Reaching the milestone of successfully completing the 200th early phase patient study performed in-house by our units over the last three years demonstrates our leading ability to help biopharmaceutical companies generate better and faster go/no-go decisions about their compounds."
Source: Parexel

ITT completes acquisition of O.I. Corporation to enhance its global analytical instrumentation business

WHITE PLAINS, N.Y., November 16, 2010 – ITT Corporation (NYSE:ITT) announced today that it has completed its previously announced acquisition of O.I. Corporation, "OI," for approximately $29 million. OI is a leading provider of innovative instrumentation for laboratory and environmental testing in the pharmaceutical, petrochemical, power and industrial markets. The company's portfolio will enhance ITT's Analytics business, which was formed earlier this year with the acquisition of Nova Analytics. "The addition of OI to our existing portfolio supports our strategy to acquire attractive companies to grow our presence in the $6 billion global analytical instrumentation market," said Chris McIntire, president of ITT Analytics. "Combining OI with our own product offering allows us to expand our technical expertise to serve our instrumentation customers, and will enable us to better serve our global customers."
Source: ITT Corporation

Best for drug trials? Thailand

Thailand has emerged as the best location for drug companies in Asia to conduct clinical trials, according to a new study by CMR, the consultancy. The country ranked as the most attractive venue to test experimental medicines on patients, with particularly high scores for both patient recruitment and quality.

The report comes as the pharmaceutical industry is showing growing interest in shifting its drug testing from North America and western Europe towards emerging markets, especially in Asia. In total, Thailand only runs a relatively small number of clinical trials, with China and Japan dominating the business - a reflection of their more established infrastructure and the appeal of their large and lucrative domestic markets.

Thailand also performed less well than other Asian countries - led by Japan - in ease of regulatory procedures. There could also be concerns that Thailand is reaching the limits of its trial capacity.
Source: CMR Consultancy

Juvenile Diabetes Research Foundation And Amylin Pharmaceuticals Partner To Investigate Metreleptin As Potential Therapy To Improve Blood Glucose

The Juvenile Diabetes Research Foundation (JDRF) and Amylin Pharmaceuticals, Inc. (Nasdaq: AMLN) announced on the 17th of Nov 2010 that they entered into a research collaboration agreement to provide financial support for a clinical proof-of-concept study to investigate the effects of metreleptin, an analog of the human hormone leptin, in patients with type 1 diabetes. Researchers at The University of Texas (UT) Southwestern Medical Center will conduct the study.

"Better blood glucose control means healthier living for people with type 1 diabetes," said Aaron Kowalski, Ph.D., Assistant Vice President of Treatment Therapies at JDRF. "If effective in humans, metreleptin, when used with insulin, could change the way people manage their disease. Less insulin usage and fewer low blood sugar episodes would represent a significant improvement in quality of life for certain people living with type 1 diabetes today."

About the Study

This proof-of-concept clinical study will investigate whether treatment with metreleptin can help improve blood sugar control and decrease the daily doses of insulin required in patients with type 1 diabetes. This is the first clinical study evaluating metreleptin treatment in patients with type 1 diabetes. The study will also evaluate whether treatment with metreleptin can improve variability in blood sugar levels, including the propensity for hypoglycemia (low blood sugar levels), which affects many people with type 1 diabetes.

Source: Juvenile Diabetes Research Foundation

Regado Biosciences, Inc. Presents Pharmacokinetic And Pharmacodynamic (PK/PD) Substudy Results From Its Phase 2b RADAR Trial

Regado Biosciences, Inc., a privately held company leading the development of antithrombotic aptamers with active control agents, announced that Thomas J. Povsic, MD, Ph.D., Duke University Medical Center, presented an abstract at the AHA Scientific Sessions meeting on November 16, 2010 at 10:45 a.m. CST in Chicago, IL.

The abstract, entitled "RB006, a Direct Factor IX Inhibitor Results in Consistent and Near Complete Inhibition of Factor IX in Patients with Acute Coronary Syndromes: A RADAR Pharmacokinetic and Pharmacodynamic Substudy," evaluated the appropriateness of the selected dose of pegnivacogin (a.k.a. RB006) for use in patients with Acute Coronary Syndromes. RB006 is part of the REG1 anticoagulation system.

The data from this abstract demonstrated that RB006 (1mg/kg, IV) results in consistent and near complete inhibition of FIX in patients with ACS with stable anti-coagulation throughout catheterization (PCI). These findings further validate the dosing of RB006 for Regado's ongoing and planned clinical trials.

Source: Regado Biosciences, Inc

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