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Foreword

I would like to take this opportunity to talk about two geographic regions: Africa and Asia. Within this issue you will find two very interesting articles; one highlighting the diversity of languages in the African continent, by Simon Andriesen, Managing Director at MediLingua, and the second covering clinical trials in China, by Chris Toller, Director of Strategic Development at ChoiceOne.

I have observed that, despite maintaining regional offices within Africa, many major drug and device manufacturers frequently overlook the continent when sponsoring clinical studies. Cultural barriers, political upheaval and uneven infrastructure are certainly causes for the lack of interest. But Africa offers tremendous expertise and opportunity for drug and device companies looking for cost-effective study sites and appropriate patient drug market populations.

As challenging as Africa may seem, drug companies have made commitments to improve healthcare across the continent, and these companies' clinical development strategies go hand-in-hand with that improvement. In coming years, the drug market and device industries will greatly expand their clinical development presence in Africa, mainly in South Africa and a select few North African nations. Make sure that your clinical strategy team has all the knowledge available about the growth opportunities in these countries; Africa presents a unique profile that interests many life sciences companies.

Of all emerging locations or regions, Africa has arguably the least access to quality care, ensuring a steady stream of dedicated patients to fill trial enrolments. In addition, the most advanced nations offer highly diverse patient populations that will translate well for submissions in the US and EU. Many major European companies are located just across the Mediterranean from North Africa, making travel and communication easier than in Latin America, for example. For American companies, Africa is much closer than Asia.

Though trial saturation is not a concern in any emerging markets yet, Africa is the least saturated of all regions. Companies that establish clinical operations bases now will be ahead of the pack when more of the industry turns to Africa.

In the Asia Pacific Region we have to harness the best of East and West to advance clinical development. Among the globe's emerging clinical research markets, Asian countries tend to offer the highest number of available patients for trial participation. The region also hosts a thriving pharmaceutical and biotechnology industry, and medical education among investigators has come in-line with Western expectations for Good Clinical Practice. As more companies move clinical trials into this region, they will benefit for years to come from its inherent expertise.

Answering some of the burning questions about Asian clinical trials, and analysing detailed data on China and India as well as information on trials in Malaysia, Hong Kong, Taiwan, Thailand, Singapore, South Korea and the Philippines, my team at Journal for Clinical Studies have learned the advantages and challenges that each of these countries presents, and use the benchmarks, metrics and best practices to avoid common pitfalls and solidify your Asian clinical trials strategy:

The first is to address intellectual property concerns in emerging clinical research markets. In the upcoming May issue, we will bring you a report on the progress made in China, India and other Asian nations around IP protection. The report will also help you navigate regulations, healthcare infrastructure, costs and patient access.

The next is to benefit from strong physician-patient relationships. Advantage should be taken of the strong physician-patient relationships created in different Asian countries. Tap into these bonds to boost enrolment and retention for your clinical studies.

Too often, companies approach specific emerging markets with regional strategies. Within the next few issues, we at JCS will provide features which will illustrate the benefits that each individual country provides so that you can develop detailed plans for running trials in each market. Tap into the best ratios of cost, quality and timelines while using local partners to navigate culture, communication and regulations.

I am sure all of you are getting ready to attend the DIA's Euromeeting in Copenhagen. The event promises some very interesting discussions on global clinical trials, and a great networking opportunity.

I hope you enjoy the diverse range of articles in this issue, and look forward to meeting you all soon.

Mark Barker
Publisher

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New Guidances Offer Insight to Biosimilarity in the US

In February, the US Food and Drug Administration (FDA) released the long-awaited biosimilarity draft guidance documents. On the day of the release, the FDA held a press conference to provide information on the publication of these guidances. At that time, the agency noted that it had received 35 pre-investigational new drug application (IND) meeting requests for 11 reference products, and had held 21 pre-IND meetings. There were nine INDs currently logged in at the FDA, and "no applications had been received as of yet."

In a formal statement, the FDA explained that the extreme complexity of large molecules making up biologic products requires careful consideration of biosimilarity and interchangeability in the production of generic biologic products. The FDA released three guidances; two that outline quality and scientific considerations, and one that answers questions regarding the approval process. To introduce the guidances, the FDA also released a companion document, "Questions and Answers: Issuance of Three Draft Guidance Documents on Biosimilar Product Development."

Directed at sponsors interested in developing biosimilar products, the guidances provide information on the FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The BPCI Act amended the Public Health Service Act (PHS Act) and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. Biosimilarity and interchangeability are considered separate standards under the law. A key point is that biosimilarity and interchangeability must be to an *FDA-approved* reference product. There is some discussion in the guidances of the potential use of bridging studies to allow for reference products that are approved outside the US. This was the focus of several questions at the FDA press conference and is reviewed in the guidances.

The guidances will assist sponsors in navigating these new processes and are designed to facilitate the approval of generic biologics. Specifically, they are intended to assist industry in understanding the FDA's approach to determining biosimilarity of products to be considered for approval in the US under section 351(k) of the PHS Act. "These are living documents and they will evolve with the science," the FDA stated during the press conference regarding the guidances:

- Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
- Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

Certain conditions for biosimilarity were required by law. For example, a definition of "protein" was made mandatory by the BPCI Act. This definition, as well as one for "chemically synthesized polypeptide," is detailed in the "Biosimilars: Questions and Answers" guidance in *Section II: Provisions Related to Requirement to Submit a BLA for a "Biological Product."* This guidance also informs on questions regarding biosimilarity versus interchangeability and exclusivity provisions in section 351(k)(7) of the PHS Act.

In general terms, the "Scientific Considerations" document provides insight into the FDA's approach to determining biosimilarity consistent with the "totality of the evidence." It includes a description of a stepped approach to developing supportive data for a product. This approach begins with extensive structural and functions characterisation of the proposed and reference products. The FDA notes in this document that the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

The "Quality Considerations" guidance provides the FDA's approach to review of analytical studies that may be used to assess whether a protein product is "highly similar" to a reference product. "Highly similar" is the terminology used to describe the measure of biosimilarity as defined in section 351(i) of the PHS Act. Specifics related to the chemistry, manufacturing, and control (CMC) aspects of the marketing application for a proposed biosimilar are described within this guidance.

Regarding review timelines, the FDA indicated at the press conference that once a product is designated biosimilar, the sponsor can pursue interchangeability. If a request for interchangeability is made in the original application, it will be part of the 10-month review clock. If this request is made after approval, it will be reviewed as a supplement to the original application. One question from the press related to future guidance. To this, the FDA responded that if specific issues arise warranting additional guidance on clinical trials for biosimilar products, the potential will be considered; at the moment, however, the agency "feels that this approach would not expedite approval."

Regina Ballinger has been with Thomson Reuters for nine years, specialising in pharmaceutical regulatory affairs. She is currently a senior regulatory intelligence manager and oversees editorial content for the IDRAC regulatory database, including the *AdComm Bulletin*. She has been employed in the healthcare industry for over 15 years.
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Cardiovascular Safety Watch Column

Last month the Cardiac Safety Research Consortium held a meeting at the FDA Headquarters in Silver Spring, MD, USA, entitled "QT Assessment in Early Clinical Development: Can the Predictive Value be Enhanced to be Similar to That of a TQT Study?"[1]. The meeting discussed the rigorous collection and analysis of electrocardiogram (ECG) data, including QT interval data, in early-phase studies in order to assess a drug's liability to prolong the QT interval. The purpose was to consider whether such an approach could eventually replace the ICH E14 Thorough QT/QTc (TQT) study that is currently the gold standard for assessing such liability[2, 3].

Part of the day-long programme also discussed non-clinical assessments, and how a more extensive battery of non-clinical tests might be considered alongside early-phase clinical data in an integrated manner that may prove even more persuasive evidence for replacing the need for a later TQT study. The FDA's Dr John Koerner gave a presentation entitled "What aspects of the non-clinical data increase confidence in this data in an integrated approach to QT data?" In his talk he said that the hERG trafficking inhibition assay would be a useful standard addition to the present non-clinical battery of tests. During the 'question & answer' session following the presentation, representatives from Health Canada and the European Medicines Agency agreed with the spirit of Dr Koerner's comments.

Ionic current flowing out of cardiomyocytes through hERG cardiac potassium ion channels embedded in the cell's plasma membrane is necessary for repolarisation of the cell following depolarisation and contraction. Reduced current leads to delayed repolarisation and the resulting QT interval prolongation, which is associated with a very rare, usually self-correcting, but potentially fatal ventricular arrhythmia called *Torsades de Pointes*. The non-clinical hERG assay and the clinical TQT study assess the degree (if any) to which drug molecules block the hERG channels and thus cause a loss-of-function, less hERG current flow, and hence impaired (delayed) repolarisation. However, another mechanism of such loss of overall function is hERG channel trafficking inhibition. If the expected complement of normal variant hERG channels does not arrive at the plasma membrane after they have been manufactured in the cell's endoplasmic reticulum, i.e., if a drug leads to hERG channel protein trafficking inhibition, the total number of channels in the cell membrane, and hence the total amount of hERG current flowing out of the cell, will be reduced, again leading to delayed repolarisation. Under normal circumstances, chaperone proteins carry out cytosolic quality control mechanisms by performing two functions[4]:

- They aid normal variant hERG proteins to fold correctly in order to be shipped to the cell's Golgi apparatus and taken to the cell membrane for correct insertion;
- They recognise and "tag" abnormal variant hERG proteins, and, whenever possible, help them to fold into the correct three-dimensional conformation so that they can then be shipped to the cell membrane as fully functioning hERG channels. If such correction is not feasible, the abnormally folded hERG proteins are sent to the proteasome for degradation.

Chaperones therefore play a critical role in hERG protein trafficking, i.e., getting the correct number of structurally correct hERG channels embedded in the cell's membrane.

Now consider the scenario in which a drug molecule interferes with the activity of chaperone proteins, thus preventing the normal complement of hERG channels being taken to, and then embedded in, the cell's plasma membrane. Such a protein trafficking deficiency would lead to a reduction in cell surface expression of hERG channels, a reduction in hERG current, and delayed repolarisation. While the mechanism of this overall loss-of-function is different, it leads to the same end result as the commonly acknowledged scenario in which drug molecules block the flow of hERG current through the channels that have been correctly embedded in the plasma membrane. hERG channel trafficking inhibition is therefore also of clinical concern.

For additional reading, a recent paper by Dennis et al.[5] is instructive, and the chapter by Ficker et al.[4] provides excellent background reading. The work of this group is a superb example of translational cardiovascular safety research, and it is placed in this context in a recent review published in this journal[6].

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What GMP-related Quality Systems Should be Available at Investigational Sites?

As described in the last issue of JCS, control of storage conditions of investigational products (IPs) is often challenging to site personnel due to lack of training and systems supporting them in this regard. But it is an ICH requirement, and highly recommended, to establish systems and training in order to ensure proper handling and storage of IPs, and to avoid rather expensive IP replacement due to failures during handling or storage. This watch page deals with questions helping investigational sites setting up a quality system preventing mishandling and wrong storage of IPs.

1. ICH Requirements

ICH E6 (R1) guideline requests in chapter 2.12 that investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

In chapter 5.14.3 it is requested that the sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s).

2. Questions to be Answered by an Effective Quality System

In the following part there are questions listed covering the process chain from IP receipt at site until dispensing to the patient. It is probably dependant on the level of cooperation between the sponsor, the investigator and site personnel how much attention is finally given to setting up and maintaining a system assuring GMP-compliant handling of the IP.

2.1 Responsible Staff

Is there a person at site being assigned as responsible for GMP-related aspects (e.g. pharmacist of the site pharmacy)?
If so, is the person responsible for standardisation of
- IP handling and storage processes
- documentation
- training?

2.2 IP Delivery to Investigational Site

Who at site will be informed in advance of a planned IP delivery?
Who will take over the IP from the courier staff (gate staff, study nurse, pharmacist)?
Where is the IP stored immediately after site delivery?
Are there any written procedures describing what to do with the IP after delivery?

2.3 Storage at Investigational Site (Pharmacy or Ward)

Is there an inventory system available, allowing retrieval of IP entrance and dispense?
Will un- or re-packaging of IP for storage reasons be documented?
Are there defined and separated storage areas for IPs waiting for dispensing to patients and for IPs returned from patients?
Have the storage areas been qualified complete with temperature mapping?
Is there a calibrated temperature surveillance system including documentation and alert?

2.4 Reconstitution and Other Processing Steps at Investigational Site (Pharmacy or Ward)

What processing steps is the site allowed to perform?
Are there hygiene instructions appropriate for each process step (e.g. cleaning of rooms and equipment, clothing, microbial monitoring, air change rate)?
Are there logbooks for equipment to document usage and regular calibration (e.g. balances)?
Are there instructions for process steps like reconstitution, repackaging or relabelling?

2.5 Delivery to Ward Personnel and Dispensing to Patients

Are study nurses trained with regard to
- storage and handling requirements of the IP in their ward,
- preparation of IP like reconstitution and GMP-compliant documentation,
- informing patients on IP aspects to be considered by the patients (e.g. storage condition, expiry date, explanation of booklet label)?

2.6 Dealing with Deviations

Are there instructions on how to deal with deviations (e.g. documentation of deviations, information of investigator or sponsor, quarantining IP until deviation has been assessed)?
Have the different types of deviations been defined and explained to site staff (sometimes deviations are not recognised as such, like temperature deviations outside of 2-8°C)?
Is site staff well trained on deviations, how to document them and whom to inform by when?

3. Conclusion

Although there is a certain lack of national regulation with regard to GMP requirements to be applied in investigational sites, sponsors and investigators are well advised to adhere to the guidance given by ICH E6 (R1) in order to prevent the unintended and unnecessary impact on expensive IPs waiting for their application with patients.

Dr. Claudio Alexander Lorck has over 23 years experience in the field of Clinical Trial supply management. Having started his pharmaceutical career in Pharmaceutical Development, he held responsible positions in QC and R&D at Fujisawa Deutschland GmbH and Astellas Deutschland GmbH. Claudio now heads the business unit of "Clinical Trial Materials" of Temmler Werke GmbH delivering supply services for clinical trials all over the world. **Email: lorck.c@temmler.eu**

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Using the Relationship to Motivate

Steve Knight, one of his company's newly promoted clinical project managers, sighs as he looks at the Gantt charts pinned to his office wall. The charts show an elegant plan, agreed by all of the key players, to hit a key milestone by late spring.

Seeing the progress reports this morning, it's clear that's never going to happen.

As he wonders how he will break the news to the Clinical Operations VP, he reflects on how well organised everything seemed last year.

A well respected CRO, MedSolve Inc, signed the deal in June to run two of the company's largest Phase III trials. At the time, everyone was happy. The bid defence meeting was excellent. Medsolve came highly recommended and their price was competitive. Their risk management and proposed communication regime especially impressed company senior managers. Steve was pleased that Medsolve's project manager and core team seemed particularly enthusiastic and aware of the key drivers for success.

Since then, two unfortunate developments are causing Steve to wonder whether the deal was such a good one.

Firstly, that great project manager has left, and so have some of the Medsolve core team. Secondly, recent reports from local company staff in several of the key countries are expressing quite negative views about the work level of the Medsolve CRAs, saying that they are failing to push on the centres; frequently it seems they have the attitude that 'it will wait until next week' just at the time when everything is really urgent.

Steve knows that his management is likely to be very unsupportive of Medsolve. The CRO have signed the deal, are being paid, and should deliver what was promised. He wonders how gullible he must have been in allowing a fairly free reign to the project manager.

What would you do if you were Steve? Probably you'd have to start monitoring them much more closely. You'd have to ask them urgently to explain what they are doing day to day and urge them to accelerate in each area of detail.

In his situation, it's likely we'd have to do the same thing. But the luxury of this being a magazine article is that we can travel back in time. *What could you do to prevent this happening in the first place?*

Can We Do Anything at the Start?

Many companies have had experiences like this, and understandably are wary of the same thing happening again, **it's only natural to build in close supervision from the outset.** There is another natural response – to build or purchase IT systems to record, measure and communicate activity at a very detailed level.

But before we do this, let's hear the story from the CRO side. Many CROs that are trying to win big contracts may 'oversell' their capabilities to deliver. Talented staff are in demand with their competitors who are hunting the biggest strategic deals. What Steve may find out if he asks (but they may not volunteer this) is that Medsolve staff's motivation to go the extra mile for clients is compromised from the start by a deal their commercial guys have negotiated, that they think is unfeasibly difficult to deliver. If he sets out to micro-manage from the word go, it may make him and his senior managers feel better, but in performance terms, could have no effect at all or might even make things worse.

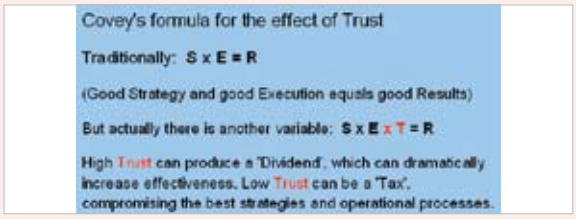
But what can we do? We have to generate some reasonable level of confidence that we can achieve what we want to!

We suggest two things – firstly, to build a partner relationship based on trust. Although this is a challenge, many companies are thinking in this way. Secondly - and this is the one where often it seems we have forgotten some common sense - build genuine motivation and engagement into the team of players on both sides. We would do well to use some techniques that have been around for decades.

Trust is a Power Tool – Powerful and Scary!

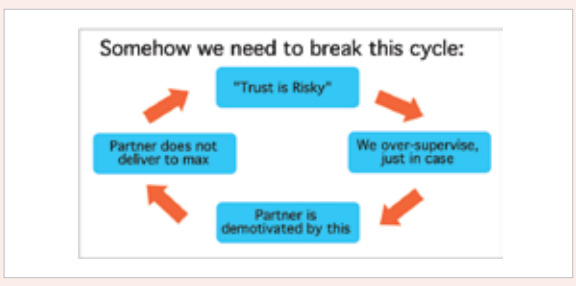
We've met many people in pharma companies who have said that you "can't" trust people outside of the company. But we would say that building trust is a very good idea, just so long as we remember a few things. Sponsors can't delegate away oversight, which is a regulatory requirement. But they can stop supervising detailed aspects of peoples' day jobs, which they can do perfectly well themselves, and invest them with some proper responsibility.

Trust is more than a 'nice to have' which builds over time. It can be built more quickly than you'd think, really help to tap into the motivation of people, and eventually, produce great results. See the illustration in Fig. 1.



Everyone has horror stories about trust. These may be based on gullibility, too much trust, where we've believed enthusiastic promises, failed to check facts and been disappointed. Or on suspicion, too little trust, where we've been over-cautious and missed an opportunity.

It's important, if a little scary, to talk about it openly, with a mindset that assumes people are basically honest, supportive and desirous of performing well.



It can be difficult to make a case to operate in this way, particularly in regard of giving autonomy and increased responsibilities to CROs. The all pervasive 'But just in case....' from a senior manager can so easily demand the sort of micro-management that our industry is well known for. However, the signs are that two industry trends are pushing this way of operating more to the meeting table:

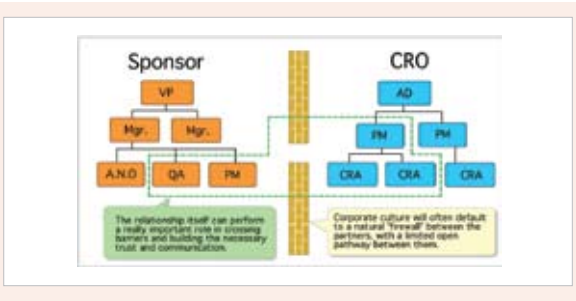
Firstly, mid-sized pharma companies are looking at new models, top-down. Several of the companies we have seen are looking at the financial benefits of smaller internal teams, having the CROs involved at a very early stage, writing trial protocols. The sort of values of trust and motivation are being expressed by CEOs and clinical directors.

Secondly, the CROs themselves are becoming ever more persuasive and powerful. Several we know have expressed the view that they can take the lead in all of the relationship management with a sponsor, leaving the pharma company just to get on with the science and other functional aspects.

How Do We Get People to be Motivated and Engaged?

We can't generate extra resources by magic. But we can motivate, not by keeping people happy, or by using social events, perks or bonuses. What we need to do is to *get everyone to work as hard as possible, driven by the challenge of achieving our goals.*

Encouraging this type of attitude is supposed to be the responsibility of the sponsor's and the CRO's managerial structures. They take charge of individuals' performance management and development. But their performance focus may well miss some of the key motivating factors.

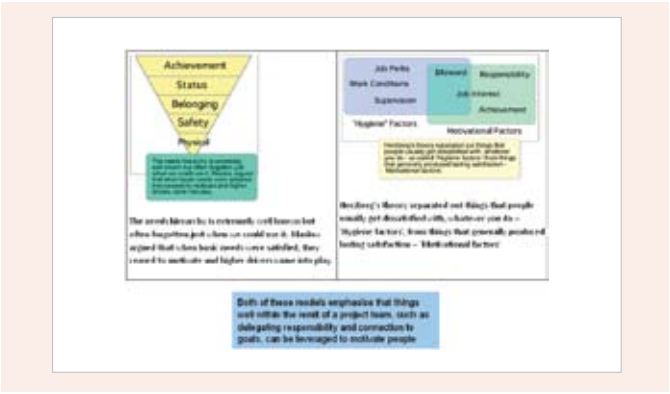


What do you think of your senior management? Odds on you don't hero-worship them. It is not uncommon for people to be highly enthusiastic about their professional work, closely bonded with colleagues in the same functional area, but unappreciative of senior execs' leadership. Thinkers in the human resources world say that organisation membership typically produces *commitment* (a feeling of duty to work in return for pay) rather than *engagement* (a sharing in enthusiasm for business goals and a drive to achieve them).

The good part is that the things that are known to generate motivation and engagement can be addressed in another dimension - the 'horizontal' project team structure that manages things day-to-day.

For 30 years or more, organisations' basic leadership training courses have introduced motivational theories and models that still have huge relevance today.

From two of the oldest - Abraham Maslow's Hierarchy of Needs and Frederick Herzberg's 'Motivation-Hygiene' theory - we can infer the same message: money-based attempts to motivate such as increased fees and bonuses, or threatened removal of them, while being very important to businesses as a whole, provide some, but not a great deal of motivation for individuals.



The needs hierarchy is extremely well known but often forgotten just when we could use it. Maslow argued that when basic needs were satisfied, they ceased to motivate and higher drivers came into play.

Herzberg's theory separated out things that people usually get dissatisfied with, whatever you do – 'Hygiene factors', from things that generally produced lasting satisfaction – 'Motivational factors'

In fact, validated research by US economists showed that there are three things that really do produce engagement with work. Autonomy – self-direction is good; Mastery – people love to do what they are good at, and can get better at; plus Purpose - people benefit by being connected to an overall, longer-term goal. All of these things are to a great extent 'free' and can be tapped into to great benefit.

What can be Done Right Now?

Whatever culture you find yourself in, if you are an outsourcing manager or clinical exec, like poor Steve in the opening section of this article, there are some really helpful things you can do.

Change something even if you can't change the world. You can't fight city hall. You may not have influence over the way top management operates. But most project managers we meet have a lot of leeway and they're still far too risk-averse when it comes to trust.

Discuss the goals in depth. Not just the CRO deliverables, but try to make everyone understand the sponsor business objective. What are the various commercial and healthcare drivers for a new drug? What is particularly important out there in the key opinion leader community, and so on. If possible, get your top scientists to come and talk.

Plan a regime of communication. Who alerts whom, when what happens, and so on. Let the CRO drive some of the communication. Why not let them prepare agendas for meetings in advance? Trusting people never means that they don't let you know what's going on.

Complete a thorough stakeholder analysis, together. Sure, there are difficult characters in your senior team. Treat them like customers. Help people to understand what their position is, what their personality is, how best to influence them.

Complete a risk assessment, together. Don't forget you can use this as a powerful influencing tactic. Not only can you flag up what horrible losses might occur, but you can also have a plan ready. Risk assessment is of course a standard part of managing studies, it's just that it's often not done very well. Somehow, you have to get the more junior people in the extended team involved, and coming up with possible 'what might go wrong's. It's these guys that will give you the real value.

Talk about the relationship. Take time to ask what's going well and why. What hasn't worked well, why, and what are we going to do about it.

Get someone in to help you with the above. An independent facilitator can really help you make progress.

Measure the relationship. There are ways and means of assessing the health of a relationship. It's a great idea to get an outside pair of eyes to observe your team in action, and/or you can use an online assessment.

Hopefully, if we went back to one of Steve's extended team meetings in a few years' time, we would see a changed landscape. There would be no painstaking review of detailed site data, or line-by-line checking of SOPs. It would focus on only two of three things. *Risk* – reviewing the rolling risk register; *Major decisions* – what the team needed to do to influence the sponsor senior team to keep the project evolving; *Learning* – how are things going, how can we continue to get better. With time for coffee, and a nice lunch!

John Faulkes began his career as a scientist in the pharma industry, then in HR as an L&D business partner, before working as a consultant specialising in cross-functional collaboration, and project leadership. John helps companies to develop ways to work in effective business relationships, and coaches and facilitates teams and team leaders. He also has designed an innovative online relationship health assessment tool that helps teams to review progress and make continuous improvements. Email: john.faulkes@ppmld.com

DSUR: A Review of this New Aggregate Safety Report and the Risk Management Perspectives

Introduction to the DSUR

Periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects, as well as to understand the benefit-risk of any medicinal product. A Periodic Safety Update Report (PSUR) fulfils national and regional requirements for periodic reporting on the safety of approved drugs. For drugs under development, currently, laws and regulations of some ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) countries and regions require submission of a periodic safety report to regulatory authorities. However, significant differences in the CONTENT, FORMAT and TIMING of these reports highlight the importance of harmonisation and a common standard report. Based on CIOMS (Council for International Organizations of Medical Sciences) VII recommendations and the ICH E2F guidance[1], the Development Safety Update Report (DSUR) has been created to be the common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. In the European Union / European Economic Area (EU/EEA), the guideline has become effective from 1 September 2011[2]. The United States (US) and Japan have not yet incorporated the guideline into national law. Nevertheless, the FDA may accept a DSUR when a request for a waiver has been submitted and approved beforehand. Consequently, the DSUR has replaced the EU Annual Safety Report and may replace the US IND Annual Report[3].

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period, related to a drug under investigation, whether or not it is marketed, by:

(1) examining whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety;
(2) describing new safety issues that could have an impact on the protection of clinical trial subjects;
(3) summarising the current understanding and management of identified and potential risks; and
(4) providing an update on the status of the clinical investigation/development programme and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug.

Operational Aspects

A single DSUR should be prepared for an investigational drug encompassing:

- All strengths
- All formulations
- All indications
- All patient populations under study

This includes sponsors with multiple clinical trials, multiple sponsors in formal agreements as well as sponsors of combination products. The focus is on clinical trials of investigational drugs (including vaccines and biologics) for the period under review. Comparator information may be provided if relevant to the safety of trial participants. The DSUR should also include significant safety findings arising out of other sources such as non-clinical studies, epidemiological studies, manufacturing changes and others. When a single DSUR cannot be prepared, the rationale for separate DSURs should be provided in each report.

The Development International Birth Date (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide. The data lock point (DLP) of the DSUR should be the last day of the one-year reporting period. The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR data lock point. Where national or regional laws or regulations require submission of an annual safety report on an investigational drug to ethics committees/institutional review boards, the DSUR Executive Summary might be appropriate, supplemented with line listings of serious adverse reactions (SARs) as warranted. DSURs should continue to be submitted for as long as indicated by national or regional laws or regulations. For example, in the US, sponsors might keep an IND open even if no clinical trials are ongoing or planned. Annual reports are submitted for as long as the IND remains open. Sponsors should indicate that the final DSUR serves as the last annual report for the investigational drug in that country or region and also indicate whether or not clinical trials are continuing elsewhere.

The sponsor of a clinical trial is considered responsible for the preparation, content and submission of a DSUR. The sponsor can delegate the preparation of the DSUR to a third party (e.g., a contract research organisation). The investigator's brochure (IB) in effect at the start of the reporting period should be used as the reference safety information. If the IB has been revised during the reporting period, a copy of the current version of the IB should be provided as an attachment to the DSUR. The Local Product Label can be used when an IB is not required as per national or local laws.

EU-ASR vs. DSUR – The Differences

The differences between the former EU-ASR and the new DSUR could be summarised as follows:

EU-ASR	DSUR
Based on first authorisation of a clinical trial of an investigational medicinal product (IMP) by authority in any EU member state	Based on the DIBD of the IMP
Clinical trial data	Additional relevant safety information from ➢ non-interventional studies ➢ marketing experience ➢ other DSURs, etc
No requirement for a literature review	Annual literature review required
Assessment done for period under review	Assessment includes cumulative data from DIBD
Appendices (study-specific)	Appendices (including regional appendices)

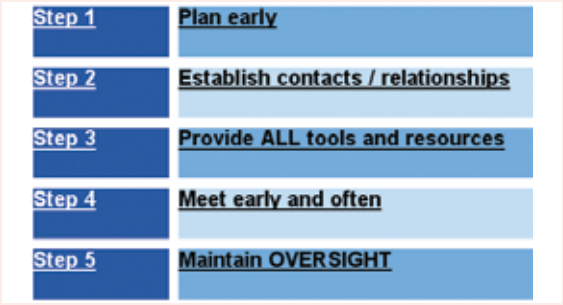
Strategies for Success

The challenges to producing and submitting a complete, comprehensive and high quality DSUR are quite varied. Time, resources, planning, project leadership and teamwork are some of the general constraints, whereas data acquisition and issues related to the DIBD and waiver from the FDA are challenges specific to a DSUR.

If a company decides to prepare the DSURs internally, the first strategy would be to plan early. It is advisable to set up a yearly calendar, identifying the number of reports to be written per year and the complexity of each report. Once the tasks are detailed out, the next step would be to identify the resources, both actual and potential, and the training required. Lead authors require significant training on regulatory documents, internal processes and procedures, access and user training in the various technologies employed to gather, collect, and present data. In addition, project management is a key to success, and effective project managers can help define roles and responsibilities, ensure close interdisciplinary cooperation and obtain senior management support when needed.

Outsourcing, whether offshoring or nearshoring, has become a part and parcel of today's working world. Apart from the obvious financial considerations, there is also the availability of highly skilled professionals and experience in the vendor staff, who are possibly already trained or can be easily trained on sponsors' procedures and technology. These professionals complete defined tasks only and can be available as and when required.

As careful planning internally minimises effort and maximises outcomes, outsourcing also requires careful planning. The following steps, if employed, could ensure a high quality deliverable from an outsource partner:



DSUR and Risk Management

A Tool for Risk Identification

Regular and timely review, appraisal and communication of safety information are critical to risk management during the clinical development of drugs.

The DSUR provides an opportunity to review
- Individual case assessments
- Non-clinical data
- Literature (e.g. issues relating to pharmacological class)
- Cumulative data

DSURs help formally review data that have been received in the period of the report, in addition to a cumulative review of certain data, such as SUSARs, and are, therefore, an **important tool of a sponsor's signal detection system.**

A Tool for Risk Evaluation & Communication

By conducting an overall appraisal of safety data at regular intervals, RISKS can be:

The DSUR allows us to discuss what was learnt about the safety of the product in the last year, how risk was managed, what actions were taken and changes made, as well as any potential issues that need to be addressed. The following sections of the DSUR help us in presenting this data:
- Overall safety assessment
- Evaluation of the risks
- Benefit-risk considerations
- Summary of important risks

A Tool for Risk Minimisation

No, the DSUR is not a tool for risk minimisation, but findings from the DSUR can lead to:

- Protocol modifications for safety or efficacy concerns
- Restrictions in study population or indications
- Changes to informed consent for safety issues
- Formulation changes for safety
- Addition of special reporting requirements
- Plans for new safety trials

Interface with the EU Risk Management Plan

The Summary of Important Risks section in the DSUR can provide the basis for the **SAFETY SPECIFICATION OF A RISK MANAGEMENT PLAN**. The following example, taken from the guidance document, illustrates how potential and identified risks can be presented in a DSUR.

Summary of Prior and Ongoing Important Risks

POTENTIAL RISKS	PRECLINICAL DATA	CLINICAL DATA	ACTIONS
Liver toxicity	Animal study: mild hepatic inflammation	Phase I-II clinical studies: liver injury not evident	Phase III clinical trial protocols have been amended to manage potential risk of liver injury to trial subjects
IDENTIFIED RISKS	**PRECLINICAL DATA**	**CLINICAL DATA**	**ACTIONS**
None identified	Not applicable	Not applicable	Not applicable

Conclusions

The ICH E2F guideline recommended Development Safety Update Report (DSUR) will become the common standard for periodic reporting of drugs under development (including marketed drugs that are under further study) in the ICH regions. In the EEA, this guideline is effective as of 1 September 2011. It is also acceptable in many other countries outside the ICH region which used to accept the EU-ASR previously. DSURs provide an opportunity for sponsors to formally review data from various sources and to assess them for their relevance to the safety profile of the drug. This periodic review and analysis of relevant cumulative data is a useful tool for identifying and assessing risks during the clinical drug development process, and for the understanding of the benefit-risk balance of the investigational medicinal product. Additionally, the DSUR acts as a tool for communication of safety information to health authorities, ethics committees and other stakeholders.

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Dr. Hemendra Misra is a pharmacovigilance physician with more than 15 years of international work experience. His medical practice includes positions at hospitals in India and with Medecines Sans Frontieres (Doctors Without Borders). He gained public health experience as a Consultant for a WHO Anti-Malaria program in India, being part of the STB SARS Containment Team in Singapore as well as working for the Health Promotion Board in Singapore. He has more than seven years of experience in the Industry (both Pharma and CRO) as a medical monitor, drug safety physician and also leading the Medical/Safety unit in the Asia-Pacific region. Focused drug safety experience includes safety-surveillance of marketed drugs as well as drugs in development: case assessments, signal detection and evaluation, risk management activities, aggregate safety reports as well as regulatory expertise and support. Dr. Misra studied Medicine in India and has a Masters degree in Public Health and an additional Masters degree in Clinical Science both from Singapore. He is experienced in a broad range of therapeutic areas including endocrinology, CVD, infectious diseases, oncology and CNS.

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PEER REVIEWED

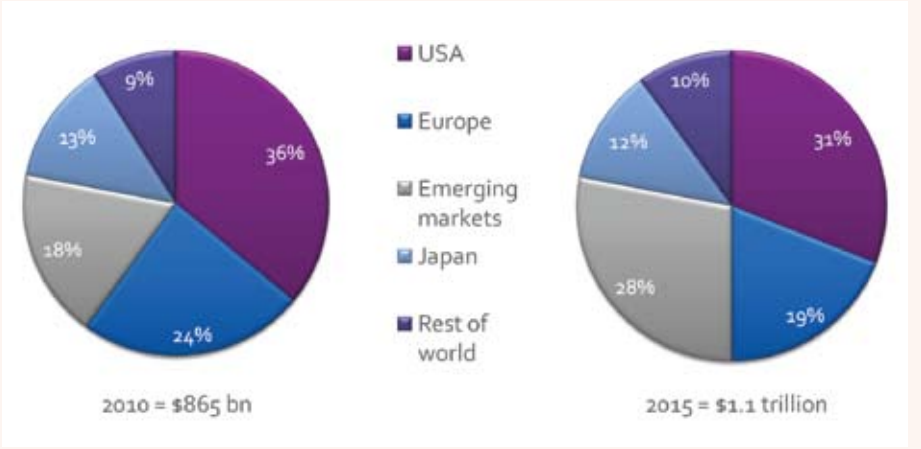
"A riddle wrapped in a mystery inside an enigma."

When he made his radio broadcast in October 1939, Churchill knew full well that Russia's response to the emerging crisis in Europe would have important implications for the world. His frustration was in having only a superficial knowledge of Russian culture and no real idea of the inner motivations of the Russian people. Without that vital understanding, he felt unable to forecast with any certainty what the future would hold. From many of the discussions I've had over the past year, I've gained the distinct impression that a lot of pharma decision-makers share the same frustrations when getting to grips with the changing healthcare landscape in China.

We all know that the Chinese market, with its dynamic economy, vast population and cultural tenacity, has the potential to have a major impact on our business futures. However, for many it is not always clear how best to turn that potential into reality.

For more than a decade, Western economies have been looking to reduce spiralling healthcare costs, and these pressures have been made even greater by the deepest global economic recession in a generation. Moreover, big pharma is facing a series of immediate pressures from the 'patent cliff' as many of the world's biggest-grossing pharma products, including Lipitor (November 2011) and Plavix (May 2012), come off patent. It is estimated that 44% of top 20 pharma companies' sales are at risk to generic competition from 2009-2014. In terms of market value, this equates to an estimated $186bn of patent-protected medicines that will become exposed to generic competition in 2010-2016[1] (Figure 1).

Figure 1: Changing shape of the 'global' pharma market [Scrip Pharmaceutical News]



Against this backdrop it is hardly surprising that global pharma companies are looking to the emerging markets as critical areas for their future growth. Amid the present global recession, the Chinese economy grew by 10.3% in 2010 and, according to a recent Financial Times report, it accounted for 40% of all global economic growth in 2011[2] (Table 1).

Table 1. China – some key facts [World Economic Database 2011]

Population	1.3 bn (44% urban)
GDP (2011 estimate)	$6.988 trillion
GDP per capita 2011	$5184
Annual GDP growth (2010-2011)	9.6%
% GDP on healthcare	4.3%
Health expenditure per capita	$108

Although China still spends less than 5% of its GDP on healthcare, government expenditure in the sector has grown significantly over recent years, and almost 50% of Chinese healthcare spending is accounted for by medicines[3]. In the recent past, healthcare in China has been governed by complex reimbursement and insurance policies that have differed significantly between rural and urban populations. In addition, the majority of privately paid health expenditure is paid out-of-pocket by patients. In 2009, the Chinese government launched a three-year healthcare reform plan, valued at RMB 850 bn ($US 124 bn) and aimed at delivering increased accessibility and affordability[3]. The first phase of this programme is focused on building basic facilities (including a mix of 30,000 new hospitals, care centres and clinics), expanding the public medical insurance system to cover 90% of the population and reforming the drug supply and reimbursement system[3].

With regard to pharmaceuticals, IMS predicted that China was set to become the world's third largest prescription drug market during 2011 and that the value of the prescription drug market alone will reach RMB 442.5 bn (US$70.2 bn) by 2014[3]. Other forecasts predict that the China pharmaceutical market will reach $100 billion by 2015 and $200 billion by 2020 – moving it ahead of Japan as the second largest in the world.

Alongside the strategic importance of its pharma market, China has also become a key focus for clinical trials activity – both for domestic regulatory studies and for multinational clinical trials. According to industry estimates, the global CRO market is expected to reach $US24 bn by 2012 – with the majority of growth coming from India and China[4]. Indeed, industry experts expect the Chinese CRO market to continue to grow at an annual compound rate of 33%[4].

It has been widely reported that China can offer sponsors numerous benefits as a clinical trials location. Patient recruitment can be very rapid, there is potential to deliver significantly reduced study costs and there is access to an extensive network of skilled and experienced investigators. At the same time, there has been equally widespread publicity for stories of bureaucratic delay and other causes of frustration

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and confusion. In this article, we will take another look at the clinical trials landscape in China in an attempt to shed a little more light on the enigma and hopefully to propose some possible solutions to the riddle.

Regulatory Issues

All clinical trials must be approved by the State Food and Drug Administration (SFDA) which is directly under the Ministry of Health of the People's Republic of China.

SFDA regulations demand that clinical trials in China are undertaken only at registered clinical centres and according to the SFDA's own GCP standards. These are similar, but not identical to ICH GCP standards. It may therefore be important for global sponsors conducting multinational trials to ensure that their studies adhere to standards that will be acceptable not only to the SFDA but also to the FDA. Over recent years, the SFDA has started to refine many of its procedures and guidelines in order to align with existing ICH and FDA standards. In addition, as the climate continues to change, SFDA personnel have started to participate in international conferences and to meet with bodies such as the United States FDA and the Drug Information Association.

– and ethics committee approval can only be started after the CTA has been granted (Figure 3). This is in contrast to many other Asian markets in which CTA approval is achieved within a few months and can be carried out in parallel with ethics committee approval.

Trial applications can be considered under four types

- Domestic new drug
- Domestic generic
- Imported drug
- Multicentre international trial

Clinical trials approval linked to an NDA generally takes a minimum of 10.5 months and an average of 12 months for a chemical product or 24 months for a biological product. For generic products, CTA takes around 24 months for an imported product and 26 months for a local product. Once the CTA has been issued, the clinical trial must start within three years.

Under certain circumstances, the SFDA will consider granting special CTA approval. For example, regulations allow sponsors with improved new drugs for AIDS, cancer and orphan diseases or drugs treating diseases for which there is no effective therapy, to apply for a special CTA approval.

Figure 2. Basic structure of the Chinese State Food & Drug Administration (SFDA)

Initial CTA application is often handled on a regional basis by the Provincial Drug Administration Authorities and is then passed to the SFDA. Sample testing and standards verification is undertaken by the National Institute for the Control of Pharmaceuticals and Biological Products (NICPBP). Within the SFDA, technical review is completed by Centre for Drug Evaluation (CDE) while administrative review is handled by the Department of Drug Registration (DDR) (Figure 2).

CTA approval in China is slow – it can take well over a year

In addition, some multicentre international trials may also receive faster CTA approval – but this is not necessarily reflected in accelerated marketing authorisation.

Ethics Committee

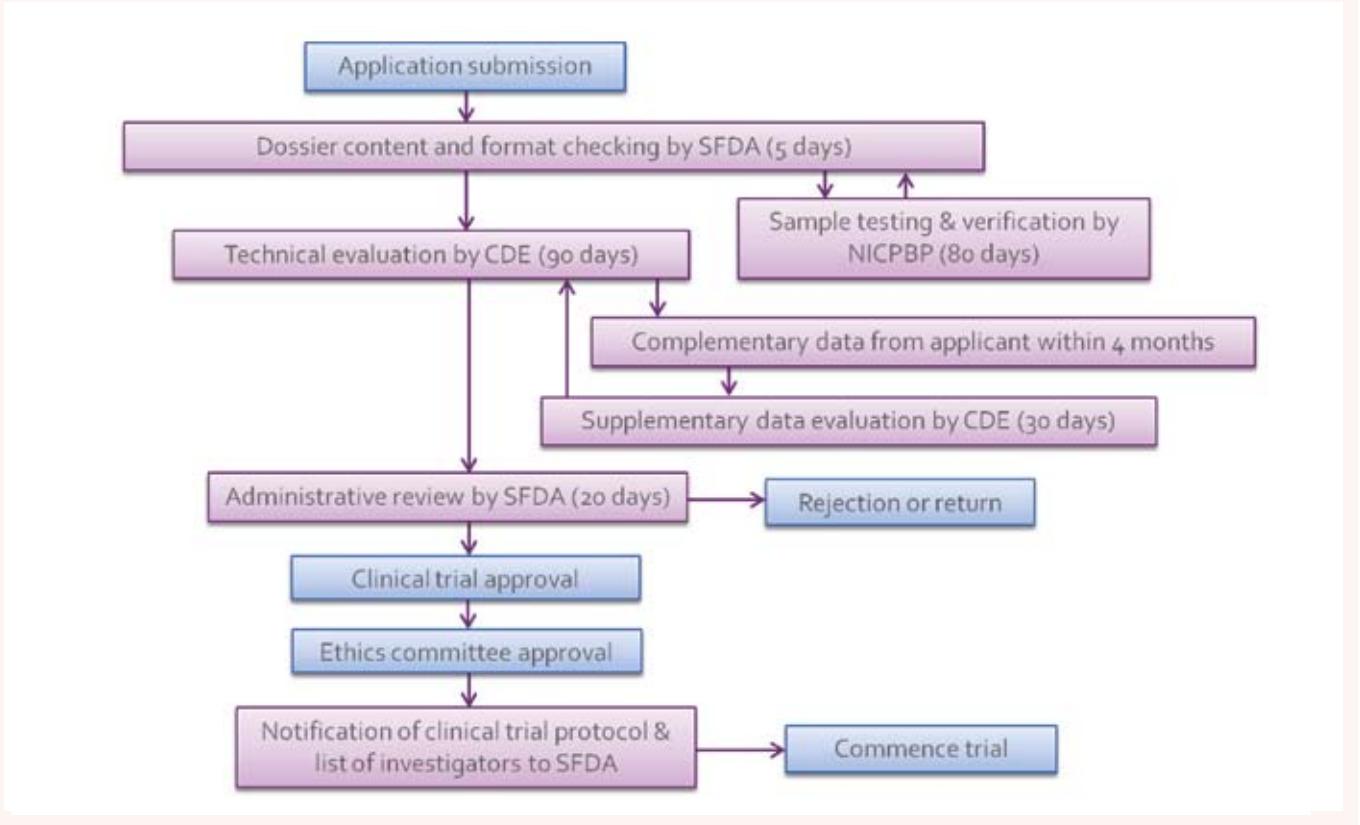
Ethics committee approval can only be sought after the CTA has been granted. The independent ethics committee (IEC) should include at least five people representing both genders, and should include at least one lawyer and at least one person not employed by the study institution.

The initial submission dossier should include:
- Application form
- Study protocol
- Investigators' brochure
- Informed consent form
- Case report form
- Regulatory approval
- Licence and GMP certificate of sponsor
- Authorisation letter from sponsor (on request)
- IMP certificate of analysis
- List of investigators
- Insurance certificate

Regulatory Strategy

Regulatory issues affecting clinical studies in China are complex, and it is far beyond the scope of an overview article such as this to provide more than a notional outline. The optimum strategy for a given product study can be influenced by so many different factors, and it is essential that regulatory issues are considered in detail early in the planning stage for any study, whether its primary purpose is domestic regulatory approval or multinational. In this context, expert national and regional regulatory affairs advice is of critical importance if undue delays are to be avoided. It is also important to take a 360° view of regulatory issues rather than building strategy on a single issue. Without this comprehensive regulatory understanding, it is possible to make decisions that will appear to 'save' a couple of months at one stage only to lose many more later on.

Figure 3. Basis of CTA application and approval process in China



Patient Recruitment & Retention

Though some aspects of regulatory bureaucracy may be a cause of frustration, China also offers huge advantages. Foremost among these is significantly improved patient recruitment and retention.

Population

At around 1.4 billion, the Chinese population has the potential to provide sponsors with almost unrivalled access to a large and important patient pool. Indeed, larger studies requiring patient stratification – particularly those demanding treatment-naïve patients – may now only be feasible in countries such as India or China. Epidemiologically, there is a diverse profile of illness and disease across the age groups, much of which reflects the difference between China's rural and urban populations. It is a fascinating observation that, while it took Western countries many centuries to urbanise, China will complete the process in a matter of decades[3]. Among those who have migrated from the countryside to the cities, the incidence of respiratory and cardiovascular diseases, diabetes, obesity and many forms of cancer has increased significantly. This trend — together with widespread tobacco consumption — is reflected in the fact that China is now reported to have the world's second highest incidence of cancer, with 2.2 million new cancer patients per year. There is also a significant and growing elderly population: in 2009, 12.5 % of the population was aged over 60, while there were over 19 million people aged over 80[3].

Limited Access to Medical Technologies

Socialised access to medical technologies is not yet widespread across China, and thus many patients will not generally have access to state-of-the-art treatments. As a consequence, it is generally much easier to find patients who are treatment-naïve. Moreover, participation in a clinical trial may well offer patients their only chance of access to modern treatment modalities.

Physician-Patient Relationships

In Chinese cultures, relationships are still largely defined on the basis of professional position, age and, to some extent, gender. Doctors are generally highly regarded, and patients will readily accept their physician's recommendation to participate in a clinical study. The vast majority of patients taking part in studies in China are enrolled as a direct result of their doctor's recommendation. By the same token, patients tend to be more compliant during the study, so that attrition rates tend to be much lower.

Linguistic and Cultural Issues

It is clear that China poses cultural, language and logistical challenges to clinical trial sponsors and to CROs.

Language

It is important to realise that, in many ways, China does not represent a single homogeneous population and that there are numerous and extensive variations in language and culture. For example, although the majority of the Chinese population speaks the official language of Mandarin (850 million), this is not the first language for many. There are several other widely-spoken languages throughout the country, including Shanghainese (90 million speakers), Min (70 million) and Cantonese (70 million)[5]. Many of the different languages of China are mutually unintelligible and most have several different dialects.

The potential impact of these language issues is significant. Most study documents must be translated into Mandarin for submission to the SFDA and to ethics committees, and this can be an exceptional examination of the translator's art. Many commonly used English phrases are not amenable to direct translation into Mandarin, and others — particularly related to the nature and severity of symptoms — will be open to widely different cultural interpretations. The burden of ensuring clear communication is significant. There are implications not only for the ethical issues associated with gaining informed consent, but also for safety and data quality. Failure among patients to understand instructions has the potential to lead to widespread protocol deviations. For example, it is important that patients clearly understand that the protocol may restrict the use of traditional Chinese remedies during the study. In addition, back-translation of questionnaires and other patient-derived information requires the same degree of precision[5].

Importance of Relationships

Good working relationships with investigators and study site personnel are important to all CROs everywhere in the world. However, In China, these relationships assume a level of importance that simply cannot be overstated. The successful conduct of a study site will often be entirely dependent on having strong relationships with the key investigators and hospital managers. From efficiently recruiting appropriate patients, through diligent implementation of the protocol to accurate recording of data, every step of the study can stand or fall on the basis of individual relationships with key personnel. These relationships are not easily won, but they are essential if project managers and CRAs are to ensure that each site will work effectively. In particular, difficult issues can only be reviewed openly and resolved effectively within the context of robust relationships built on mutual trust and respect.

Study Logistics and Practicalities

Cost Savings

China offers the potential for considerable savings in direct and indirect study costs. Chinese salaries are reported to be 60-80 % less, and clinical costs are generally 50-70 % less than those in the West (Table 2). A recent KPMG report suggested that clinical studies in China show a 70 % average cost saving compared with the USA[3].

Table 2. Example cost savings USA-China [6]

	USA	China	% saving
Blood sample	$26	$6	-77%
ECG	$103	$42	-59%
Physical examination (60 min)	$239	$97	-59%
Physical examination (15 min)	$151	$50	-67%

Clinical Infrastructure

China – particularly urban China – has a significant medical infrastructure and there is an extensive population of skilled and experienced clinical researchers. It is estimated that there are almost 70,000 hospitals and clinics in China, together with over 100,000 independent outpatient clinics. This infrastructure is reported to support over 2 bn hospital visits and 50 million in-patient stays every year. Around 80 % of medical resources are allocated to major cities and 30 % of this is focused on larger hospitals. As a result, 2000-bed hospitals are common in all major cities in China.

In February 2004, the Chinese SFDA issued a regulation stating that clinical trials could only be undertaken at authorised study sites. More than 450 hospitals have already been certified, the majority of which are in larger cities, and some of these tend to focus on particular indications, such as oncology. In addition, a number of major cities have organised clinical development

platforms incorporating certified clinical research centres, investigators and ethical committees which are geared up to undertake global trials. The United States FDA has undertaken a number of clinical site inspections in China over recent years, and in general these have found very favourable results.

Geography

The vast majority of registered clinical study centres, and indeed the majority of leading hospitals, are in major cities. Because the healthcare infrastructure in rural areas still lags somewhat behind urban development, many patients live some considerable distance from their study centre. When considered along with the limited private and public transport systems, this can mean that patients face a considerable challenge in travelling to review appointments.

Investigational Medicinal Product

Samples must be manufactured under GMP-compliant facilities and be freely supplied to study subjects.

Clinical Samples

There are restrictions to the export of whole blood products and DNA from China, and these may have important implications for certain studies.

EDC and IT Infrastructure

Over recent years, an increasing number of clinical studies in China have been incorporating the use of EDC systems. More and more investigators are becoming familiar with different EDC systems such as InForm, Rave and RDC. At the same time, however, some hospitals outside of major cities may not have reliable wireless internet connections, and access to IT infrastructure must be considered as part of study design.

CRA Training & Development

For any study sponsor or CRO, the skill, experience and dedication of CRAs is of fundamental importance. Overall, there is reported to be a relative shortage of well trained and motivated CRAs in China. In addition, there is a tendency for CRAs to move between different CROs, such that staff turnover can be high. In response to this situation, a few committed CROs have started to invest heavily in training and development for their CRAs, and are building career programmes which are paying dividends in terms of increased staff retention. These programmes help to develop valuable CRA capabilities, and the resultant stability and consistency are invaluable as they help to preserve and strengthen professional relationships with key investigators.

At Choice Pharma, we consider that CRA training and development is fundamental to our ability to uphold quality standards. Our investment in state-of-the-art training systems and an integrated career development programme contribute to our sector-leading staff turnover of just 8%. Our team therefore has stable, long-term relationships with leading investigators and these deliver huge benefits to all aspects of study management.

In summary, it is clear that China is a major and growing location for clinical trials. An enormous pool of potential patients covering the whole spectrum of indications virtually guarantees rapid recruitment. What's more, since patients are usually well motivated, retention rates tend to be high. Study costs are generally less than half those in EU or USA, and there is a large population of highly educated and experienced investigators. On the other hand, regulatory systems and procedures can be complex and protracted. As a result it is vitally important to consider the potential requirement for China studies as a priority within clinical development strategies. As a reflection of Chinese society, strong working relationships with study sites and investigators are of critical importance throughout the study. Cultural and linguistic differences mean that effective communication is frequently an important challenge that can have ethical, safety and data quality implications.

Getting the most from these opportunities requires local expertise and experience. Many sponsors have found that partnerships with specialist regional CROs have the potential to deliver the most cost-effective outcomes for their clinical development plans in Asia-Pacific.

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Medical Translators' Training for African Languages

PEER REVIEWED

Why would Africa be a linguistic nightmare? Everybody speaks English or French, don't they? No, they don't, as Simon Andriesen discusses in this article. English and French are spoken by the elite and if you need a representative sample from the population for a trial, you have to go down the language ladder a few steps. His company builds translation capacity for 100s of local languages, by training non-translators to become healthcare translators and by putting them to work in teams.

Africa – a Linguist's Playground?

For language people, Africa is the place to be. With over 2000 languages[1] spoken across 54 countries, Africa is the continent with most of the world's 6909 languages[2]. In countries such as Cameroon, around 300 languages are spoken (more than in all of Europe). For practical purposes, international companies (such as Microsoft and Google) target 'only' 85 languages, which together cover the majority of the population of Africa. If you want to further reduce the number of languages, you might be tempted to look at the official languages of the various countries: the total is around 30 languages, and that includes the 11 official languages of South Africa. However, if you hope to reach a large proportion of the population, using only the official languages will not take you far.

Many countries in Africa have selected one or two languages as their official languages, and often this includes the language from the colonial era: English or French, and to a lesser extent Portuguese or Spanish. The advantage of English or French is that it serves as a tool for people who cannot otherwise communicate with each other, which is the case in countries where several dozens (Kenya) or several hundreds (Nigeria, Cameroon) of languages are spoken. Also, English or French are 'neutral' languages and not sensitive, as would be the case if the language of the leading tribe would have been chosen. The disadvantage of English or French, however, is that speaking the official language requires some level of education, which is not within everybody's reach. It is understood by researchers that at best a small minority of the population speaks the official language of their country. This means that a large majority does not! And the United Nations Development Program (UNDP) has calculated that the similar percentages are true concerning access to education in the local language: this is the case for at best 25 % of the population. The rest are educated in a language that is not their own.

Cause of Death: Lack of Language Skills

Africa is assumed to be the origin of humans, but so far this head start has not given the continent many advantages. With a population of around 1 billion, Africa has some 15 % of the world's population, but also around 25 % of the world's disease cases, to be treated by less than 3 % of the world's doctors and nurses.

In many African countries people die not only of a disease, but often for lack of health information in a language they understand. Simple information, for example about what to do when a baby has diarrhea, can save the baby's life if it could be understood by the parents, especially if these parents believe the tale that it is best to not give water to a baby with diarrhea "as it will immediately come out at the other end, and that way it never stops". Withholding water from a baby with diarrhea will soon lead to dehydration and the next stop is death, which is a high price to pay for your parents' not understanding English.

The UN Millennium Goals[3] and the initiative Health Information For All by 2015 (HIFA2015)[4] both suggest that education and increased health literacy are important vehicles to reach many of the set targets. However, far too little attention is paid to the role of local languages. Health information in English is great for people who speak English, but for those who do not it means the same as health information in Finnish would mean to you and me: nothing (unless, of course, you happen to speak Finnish).

Inclusion Criteria for Trials: Ignore Language!

Recruiting study participants who speak English (or French) is of course easiest. However, in order to set up and run quality clinical trials in Africa, the inclusion criteria should not include speaking a certain language. Selecting study participants who speak English (or French) means including only the elite: people with a relatively high level of education. And people with a high education will have a relatively high health literacy, which, as we all know, results in a healthier lifestyle and thanks to that, a relatively high level of health. This means that when only the elite is included, the effects of, for example, malnutrition, latent TB, history of malaria, and so forth, will not become visible and a range of interactions and side-effects will stay under the radar. And who needs post-marketing surprises and, in the worst case, product recall?

Dealing with people who do not speak your language can be complex. However, when setting up a trial in, for example, Kenya, a CRO will no doubt involve local people to help organise the trial. These will probably have good English language skills, and communicating with them is no problem. They in turn will probably be able to speak at least Swahili. For most Swahili-speaking people, this is not their first language, but the language they use to communicate with people with a different local language. Such languages are referred to as 'lingua franca'. Swahili is spoken by 75-100 million people across nine different countries in East Africa, and it is one of the two official languages in both Kenya and Tanzania (the other one being English).

Besides Swahili, local people who are involved in trials will probably also speak one (or sometimes several) of the 69 (!) local languages spoken in Kenya. Six of these local languages together cover 90 % of the 42 million population of the country, including languages such as Kikuyu (spoken in central Kenya), Kamba (East) and Luo (West). The languages spoken in Kenya either belong to the Bantu or to the Nilotic language family. Languages in the same family have similarities, but that does not mean that people will understand each other if they speak their own language (just as French and Spanish people do not

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understand each other if they speak their own language). So, if these six major local languages are taken into account, a trial can really include very many people. So, if a CRO decides to set up a trial in Kenya (but the same is true in most other African countries) it would make a lot of sense to involve speakers from several of the larger local languages, and not just English.

Speakers of a local language who also have a good command of English, but who have never translated, can be trained into the ins and out of translation. Translation in itself is not that difficult. Here are the main requirements: good command of the source language (usually English), and excellent command of the target language (their own language). What makes translation hard are often external factors: a poorly written and therefore unclear source text, use of terms that the translator is not familiar with, use of terms that have no equivalent in the target language, or use of terms or concepts that are perfectly normal in English but can be unacceptable in a target language area.

Translator Training

We have developed a Healthcare Translators' Training course, and on behalf of Translators without Borders[5] we have tailored it to be suitable for people who never have translated before - at least, not that they were aware of, because bilingual people in areas with poor language skills are continuously asked to translate. One of our connections in the Masaai region (Kenya) who takes his mother to a clinic every few months, mentioned that after the doctor's appointment, it takes hours for him to leave the clinic, as many other patients, who sense he speaks English, urge him to come in 'for just a minute' to explain to them what the English-speaking doctor is saying. He ends up conveying dramatic news to patients, about a mother's baby who will not be born alive, about a man having a form of cancer that cannot be cured and will probably be fatal in six to 12 weeks, about a limb that has to be amputated, or about a delivery that will have complications caused by the genital scarring that resulted from FGM (female genital mutilation).

It is exactly this type of people, with a good command of English and of their local language (or Swahili), who can be trained to translate many types of healthcare information. About hygiene, about how to prevent cholera, about unwanted pregnancies, or, if that is too late, about how to stay away from unsafe abortions, or how to convince parents to stop FGM (or grandparents, as in some areas these are heavily involved in these decisions). During a course of two weeks (with two months in between) we teach trainees the basics of translation, including how to build their own glossary and a range of tips and tricks. We also teach them about a dozen or so Africa-relevant medical topics, such as diarrhea, pneumonia, malaria, HIV prevention, and a range of public health issues, including vaccination, clean water and waste water management. This gives them a basic level of medical know-how, and they get introduced to medical terminology. One of the training modules is *Introduction to Clinical Trial Documents*. During this module, trainees are introduced to informed consent forms, questionnaires, protocols and how to properly translate these.

After the first introductory training week the trainees will translate a volume of English health information and trial-related documents into Swahili or into their local language. This 'homework' is then reviewed and edited and will be discussed at the start of the second training week, two months later.

African language families

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

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

Typical trial documents

- Informed consent form
- Study protocol
- Questionnaire
- Instructions for trial nurses
- Instructions for investigators

After completion of the course, the trainees are available for anyone who needs them, including CROs who need local language versions of study information, informed consent forms, questionnaires, instructions for nurses and investigators, and what have you.

These new translators are trained to work in teams. The initial translation is made by translator A, and this translation is reviewed by translator B. They keep discussing the text until both agree on the (for them) final version. The text is then sent to translator C, who is a more experienced translator, and who will review this version and compare it with the English original. Any changes will be fed back to the original translators and after they agree on all recommended changes, this will be the version that will then be tested.

For such a test, we define the key safety aspects and based on these, we draw up a list of questions. A group of between three and 10 persons who are representative of the target audience are then invited to read the translation and to answer the various questions. If all participants answer all questions without a problem, the text is apparently clear enough. If several participants would need more time or effort to correctly answer a certain question, there is probably something wrong with the way the related information is presented. The text then needs to be revised and tested again. Once a text has survived all this, the document is apparently

clear enough and can be used.

By providing this in-country training, we have shown that translation capacity can in fact be created. At relatively low cost (Eur 250-750 per trainee, depending on the language) people can be trained to become translators, and if they then work in teams they will soon become good enough to work independently. The fact that few translators are available for even commonly used African languages, and that hardly any translators exist for many of the other African languages, does no longer have to be the excuse for including only English or French speaking subjects in clinical trials.

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Cell-based Immunotherapy of Hematological Malignancies using Natural Killer Cells

PEER REVIEWED

Competence Centre for Cancer Research is a body that brings together most of the organisations involved in cancer research and treatment in Estonia. Our partners include the biggest hospital in Estonia, North Estonian Medical Centre, Tallinn Technical University, Tartu University and 10 biotechnology and drug development companies. There are also industry partners from Sweden and the USA. The project portfolio of the Competence Centre for Cancer Research includes both early stage drug development projects and projects that are already in the clinical phase. Close collaboration with medical doctors enables the projects to be fine-tuned to actual clinical needs. The R&D projects of the Competence Centre for Cancer Research are funded by EU Structural Funds, Estonian governmental funds, and the partners.

One of the projects close to clinical studies is Natural Killers (NK) immunotherapy. The therapeutic potential of NK cells has been known for some decades already. However, the use of NK cells in immunotherapy has been hindered by technological difficulties in growing clinically adequate quantities of NK cells in artificial conditions. The scientists of the Competence Centre for Cancer Research have worked out a novel approach for growing NK cells even in the case of donors whose NK cells would not expand readily in conventional media. We are in the process of establishing a GMP cell-growing facility in Estonia, and expect to start with clinical studies by the end of this year. Should the clinical phase be successful, we shall be able to carry out NK immunotherapy in Estonian hospitals. With free movement of patients in the EU we shall be able to help not only local patients, but any European patients in need of NK therapy. Alternatively, we shall be able to offer GMP NK cell-growing services to research labs and hospitals in Estonia and abroad. As the needed transport conditions for NK cells can be easily met, we do not foresee major logistical challenges either. The commercialisation of NK cell therapy will be supported by the activities of Innovative Health Technologies' Cluster, Cell Therapy Cluster and Medicine Estonia – a cluster for strengthening the export of Estonian health services.

Scientists from the Competence Centre for Cancer Research have also started to study the potential applications of NK cell therapy in case of tumours other than hematological malignancies.

NK Cells Overview

Features and Discovery

Natural Killer (NK) cells are effector cells of the innate immune system. They constitute 5-15 % of the peripheral blood mononuclear cells. Morphologically they appear as large granular lymphocytes. NK cells were discovered in the 60s as the cells mediating "hybrid resistance" to transplantation. NK cells develop in the bone marrow. NK cells' functions include primary elimination of virally infected cells; immune alerting by production of various signalling cytokines, such as IFN-g, TNF-a and GMCSF; regulation of immune processes by killing immature dendritic cells; and tumour surveillance and control of metastasis. NK cells are defined immunohistochemically as CD3- CD56+ lymphocytes.

NK Cell-killing Mechanisms

NK cells can kill target cells by releasing cytotoxic granules which contain perforin and granzymes, as well as by secreting apoptosis-inducing ligands of the Tumour Necrosis Factor family. The "decision" whether to release a cytotoxic attack upon cell-cell contact depends on the balance of activation and inhibition signals received from the target cells. NK cells express multiple activating and inhibitory cell-surface receptors, often with overlapping ligand specificities. The "rules of engagement" for NK cells differ significantly from the T-cell rules, which have defined the classical adaptive immunity paradigms.

Missing Self

NK cells do not have genetically rearranged receptors like T-cells and B cells do. However, they kill the target cells with no need for previous sensitisation (Ljunggren and Kärre, 1985). Recognition of target cells by NK cells is largely based on the "missing self" concept. The missing self theory postulates that NK cells are 'primed to kill', but do not destroy normal cells because of the inhibitory signals delivered by MHC-I (Major Histocompatibility Complex I) molecules via KIR (Killer Immunoglobulin-like) receptors on NK cells. When the target cells fail to display sufficient amounts of MHC-I (as virally infected cells) or display types of MHC-I that do not match the KIR receptors on NK cells (as transplanted cells), the NK cells deliver granzyme B and perforin-mediated cytotoxic attack.

Stress Markers

NK cells do not attack epithelial tissues under physiological conditions. However, senescence and cell stress-associated molecules such as MIC-A and MIC-B induce NK-mediated lysis. NK cells also recognise Heat Shock Protein 70 on the cell surface and lyse the cells that display it. Many tumours rely on Hsp70-mediated signals for growth.

ADCC (Antibody-Dependent Cellular Cytotoxicity

NK cells have receptors for antibodies, so they can participate in the defence systems of humoral immunity, and destroy cells and bacteria covered in antibodies. NK cell ADCC is an important component of the efficacy of many modern antibody-based cancer medicines.

Pathogen-associated Molecular Patterns

NK cells also have receptors for biological molecules which are invariably associated with different microorganisms.

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These receptors are encoded in the germline DNA and have evolved in time to allow their recognition by the immune systems of multicellular orgamisms. They belong to the Toll-like Receptor family. Also, NK cells express NCR (natural cytotoxicity receptors), whose ligands are largely unknown; plus a number of other receptors which also are expressed on other types of cells, mainly T-cells. Only the NCR (NKp30, NKp44 and NKp46) are truly specific for NK cells.

NK Cell Culture Methods

The clinical studies published so far have used leukapheresis for blood mononuclear cell isolation, followed by magnetic antibody-based separation. The infused NK cell dose has been ≥1x107 CD56+/CD3- NK cells /kg with ≤1x105 contaminating CD3+ T-cells. This is the maximum amount of cells that can be collected from a donor without lymphocyte mobilisation. Larger amounts may be necessary for efficient therapy. Also, the high cost of magnetic separation makes this method unsuitable for large trials or routine clinical use. So, the NK cells should be grown *in vitro* before transplantation.

LAK Cells

The very first studies performed on NK cells used fresh cells or activated cells termed Lymphokine Activated Killers (LAK). These cells were prepared from mononuclear fractions of the peripheral blood lymphocytes by a four-day culture in RPMI-1640 media with Interleukin-2 (IL-2) and fetal calf serum (FCS). In these conditions, the NK and T-cell mixture became activated, but there was no expansion *in vitro*.

Feeder-supported System

To achieve clonal expansion of NK cells, feeder cells have been used. These are transformed cell lines - K562 (erythroleukemia) or Epstein-Barr Virus (EBV) transformed B-lymphoblasts. The feeder cells are irradiated and then mixed with the growing cells. This method provides "missing self" type of stimulation to NK cells and allows growing up to million-cell clones in about a month. For polyclonal selective NK cell expansion, HFWT cells have been used (Peng et al., 2004). Also, considerable NK cell expansion can be achieved by the use of gene-modified feeder cells. Expression of ligands for the NK cell activation receptors on the surface of the target/feeder cells can activate NK cell proliferation to a remarkable extent. Imai et al. have used K562 cells, the traditional target cells for NK, and modified them with the genes for membrane-bound IL-15 and 4-1BBL. These modified feeder cells enabled approximately a one-thousand to ten-thousand-fold expansion of NK cells in culture (Imai et al., 2005).

All methods described so far have thus relied on the use of irradiated feeder cells and fetal calf serum. It is very difficult to justify the use of cells grown in these conditions for human patients. Persistence of calf serum components on cell surface can trigger hyperacute rejection reaction, and co-culture with tumour cells or virally transformed cells can lead to immunological complications and is a risk factor for contamination. Therefore, suitable methods should be based on defined media and be free of FCS.

Expansion from Peripheral Blood

The only published method so far for growing NK cells in clinically acceptable conditions (Carlens et al., 2001) relies on growing the mononuclear fraction of blood leukocytes in CellGro SCGM medium from CellGenix GmbH with IL-2, OKT-3 (an antibody against CD3 antigen on T-cells) and human serum, and allows for NK cell expansion up to about 60x in culture, in three weeks. The disadvantages of this method are dependence on a single manufacturer of the medium, whose exact composition is secret, and large variability between donors.

However, at Competence Centre for Cancer Research, we have been able to improve the protocol significantly, which allows us to achieve high yield of NK cells even from the donors whose NK cells do not expand very well in standard CellGro medium.

These improvements allow us to move forward with a clinical trial to assess the safety and efficacy of the *in vitro* expanded NK cells.

Perspective Clinical Trial and NK-responsive Diseases

AML (Acute Myeloid Leukemia)

The first information that NK cells can have a positive effect in a clinical setting came from a retrospective analysis of AML patients who had had HSCT (hematopoietic stem cell transplantation) from a haploidentical donor. 'Haploidentical' refers to a situation where half of the donor HLA alleles match the patient, but half are mismatched (as when the donor is a sibling or a parent). Lower than expected rates of leukemia relapse in patients with AML, a lower rate of graft rejection and a paradoxical reduction in Graft-versus Host Disease (GvHD) were noted when the haploidentical graft possessed inhibitory KIRs for which the recipient had no ligand. Alloreactive NK clones that killed recipient leukaemic blasts *in vitro* were isolated from the recipient following the transplant (Ruggeri, 2002). Analysis of 40 high-risk AML patients receiving haploidentical grafts showed a significantly lower relapse rate, if the donor NK cells were capable of alloreactivity (15 vs. 68 %) (Ruggeri, 2005).

Thus, NK alloreactivity plays a major role in hematoipoietic stem cell transplantation. A suitably chosen haploidentical donor-recipient pair, displaying unidirectional NK alloreactivity, has been termed 'a perfect mismatch' situation (Kärre, 2002).

Based on the beneficial properties of the NK cells, several groups have investigated the possibility of using NK cells for donor lymphocyte infusion, with the aim of consolidating engraftment and counteracting relapse without inducing GvHD. Most of the studies have used freshly isolated NK cells from the donor, sometimes activated in culture for 1-2 days. The results show that NK cells do not cause GvHD and are capable of inducing remission (Passweg, 2005). Miller et al. have published data on infusion of donor NK cells as adoptive immunotherapy without HSCT. NK therapy is effective for inducing remission in particularly AML, whereas solid tumours and acute lymphoid leukemia are generally resistant to NK

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cell infusions in the quantities used so far. This study also demonstrated the possibility of homeostatic expansion of NK cells *in vivo* in response to high-dose chemotherapy, which was associated with elevated serum levels of IL-15 (Miller, 2005).

It is noteworthy that NK cells do not cause GvHD, which is a major complication of HSCT and a significant cause of mortality. GvHD results from donor T-cells' attack on epithelial tissues – intestines, liver and skin – which are the main sites of damage in GvHD. NK cell activities are generally restricted to the hematopoietic system and they do not attack epithelial cells unless these display stress markers, as when being virus-infected or transformed to tumour cells. In fact, NK cells may alleviate and prevent GvHD by killing the host Dendritic cells, thereby preventing the priming of the T-cells in the graft.

Conclusion

Natural Killer cells are unique in their immunological properties and can therefore be a valuable tool in the fight against cancer. By complementing the existing therepautic modalities such as chemotherapy, radiotherapy and novel protein-based antitumour agents, the NK cells can be used for direct immunotherapy or in combination with highly effective hematopoietic stem cell transplantation. After overcoming the technological hurdles of clinical-grade cell product manufacture, the clinical trial will help establish the effective dose and scheduling as well as exact indications for this novel treatment. With more than 15 years of experience in hematopoietic stem cell transplantation, Estonia is well prepared for cell therapy applications development and research.

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How Packaging Solutions are Easing Multi-site Challenges

PEER REVIEWED

Challenges experienced by multi-sites are some of the most frustrating for the clinical trial cold chain. Although trusted real-world data and profiles from around the globe have been painstakingly analysed and perfected over the years, even the most experienced and well-forecasted routes can encounter unforeseen problems. This feature provides an insight in to the challenges encountered by the clinical trial cool chain sector when transporting their precious cargo across the globe, and shares the results from the business' recent interactive presentations to the CT execs regarding issues encountered.

Defining Challenges of Multi-sites En Route

The world may be becoming an increasingly smaller place, but the different challenges it provides on every shore can be numerous, including country-specific regulations, infrastructure and customs' attitudes, and that is before the country's ambient temperature is brought into the mix. Any of these could mark the end of a clinical trial when in transit if not planned with military precision. But what happens if even still, something else crops up that you couldn't have planned for?

There has been a number of case studies that have showed us just how unpredictable clinical trial journeys in the cold chain can be. For example, even though the service provider was fully aware of the different import and export rules for shipments into Brazil, a clinical product was held up in customs due to the country's latest import/export quota, regardless of whether the shipment was a can of beans or a time- and temperature-sensitive pharma product. Essentially, clinical trials can unnervingly be out of your control when en route until they arrive in the safe hands of the intended receiver.

"However, the clinical trial industry is gladly seeing an increase of activity and innovation in new packaging solutions to overcome these problems. With revolutionary new technology we are seeing packaging that can think for itself when it encounters problems, and that can be trusted to make the right decision in a moment of crisis, saving the product from a costly and frustrating end."

Multi-award winning ZeoCool – SCA Cool Logistics' revol utionary step in the design of temperature-controlled packaging

Conducted Interactive Research

A company specializing in temperature controlled packaging, ran a series of interactive presentations in February this year at both IQPC in Basel, Switzerland, and at the VIB Cold Chain Storage & Distribution conference in London. The team at SCA Cool Logistics took the opportunity to use interactive keyboards with all audience members, asking over 500 CTS-related execs a number of questions to identify and validate key industry trends, challenges, risks and opportunities, with specific reference to transporting healthcare product in the clinical cold chain.

Question 1: What is your top priority in your temperature-assured distribution chain (apart from patient safety)?

Answers:

- Reduce or prevent product deviations or excursions = 81 %
- Ensure compliance with GDP regulations = 48 %
- Cost reduction = 41 %

With millions of dollars' worth of clinical trial product being spoilt every year due to product experiencing temperature excursions during the transportation, it is not surprising that the top priority for healthcare, integrity, logistics and distribution managers at the conference was to reduce product deviations or excursions. The smallest temperature change for even the shortest of time can make the difference between a clinical trial reaching its intended destination as a working sample or as a destroyed product.

To meet this growing need for the clinical trial market, temperature-controlled packaging products are becoming more and more intelligent. For example, reactive technology that is thermostatically controlled and can heat and cool the payload area can reduce excursions dramatically.

Where multiple investigator-sites are also involved, it relies even more heavily on the packaging to be flexible and adaptable with its performance. For example, a study that includes both Russia and Malta would need intelligent packaging to adjust to both high and low temperature extremes, which it can do easily with its incredible in-built thermostatically controlled heating and cooling technology, maintaining the desired internal payload temperature by reacting to external ambient temperatures.

Compliance with GDP regulations is a complex and constantly evolving area of expertise.

Whether this is outsourced or you have own in-house specialist, it's an important cost to the business. Failure to adhere to the latest regulations can significantly impact a trial's progress, a hard cost to measure in this arena. Yet a small investment in other areas such as packaging can go a long way in minimising the hidden cost of a delayed study.

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Whilst the actual business of staying abreast of import and export regulations lies with the sponsor and the clinical services provider, packaging itself can play a useful part in supporting the product whilst any delays occur.

David Johnson explains: "Some sponsors opt to play safe and pay a premium by selecting a specific courier who can be in sole charge of their product whilst in transit, ensuring that it is rushed through customs and reaches its destination in the shortest time possible. With intelligent packaging, this additional attention and cost is not required as the packaging can control its own temperature for up to five days, and even be placed into a fridge to prolong its duration. The costly 1-2-1 courier can be swapped for a 3PL yet the risk stays at a minimum."

Hibernation is a revelation in recent packaging offerings, allowing packaging systems to save energy, enabling it to last even longer. The packaging can be placed into a fridge during its wait between sites and the zero temperature differentials between the internal and external temperatures means virtually no energy is expended by the system.

Question 2: What is your primary distribution method used for temperature-sensitive products?

Answers:

- Air = 64 %
- Road = 28 %

With air transport leading the way, the focus on temperature-controlled packaging is on its volume, size and weight. Packaging manufacturers understand the cost implications of freight to clinical trials' distribution, and by ensuring packaging volumetric weight is reduced without impacting payload space, with some technologies now boasting up to 45 % reduction in volumetric weight, can significantly reduce distribution costs.

Multi-sites can often mean multiple freight modes are required. With intelligent packaging, once packaging systems are activated it does not matter where they are put – perfect if different modes of transport are used, which in turn provide different temperature ranges. It is good to know that regardless of the transport mode the product will be in constant safe hands.

Question 4: I am more likely than in the past to adopt new technologies or services from a supplier if it showed that if could reduce my total cost of distribution, even though the technology or service was at a higher price point.

Answer:

- 90 % agreed.

With total distribution costs being made up from packaging, freight and data loggers, there are opportunities to reduce costs through using new technologies and services, and those in the CT remit seem very open to understand these possibilities to reap the rewards.

David Johnson explains: "Knowing the full story can often help you make the most informed decision, but unfortunately this is not always the way when making decisions on distribution. For example, the sponsor may be given a cost option of either distributing using £30 or £300 boxes without the cost of freight included. Studies involving multiple investigator sites make including freight costs an impossible task. Obviously, the sponsor will opt for the perceived cheaper option to save costs, however the total freight bill could be vastly bigger because of the cheaper boxes' increased size and weight.

"An ideal world would see the service providers, sponsors and the packaging companies all sitting around one table to discuss the most efficient, low-cost option for distribution, but this unfortunately rarely happens."

Conclusion

It is not only multi-sites that have created these recent challenges. The pharmaceutical landscape has changed dramatically in recent years with the patent cliff and drying-up of blockbuster products reaching the market. Generic erosion and the lack of new products coming through has forced big pharma to change its ways, notably in the way it operates and distributes product to its growing global marketplace. Discovering efficiencies and applying lean principles are providing plenty of challenges for big pharma, and these operational challenges are intensified as the type of product shifts towards long-chain molecules and protein-based therapies. As well as being very difficult to replicate and manufacture to protect it from generic eyes, these therapies also come with strict temperature storage and distribution requirements. Now distributing product to the growing global marketplace has become a whole new ball game.

But if you could trust your packaging to make the right decisions at the right time to protect your product, the challenges discussed here are significantly reduced, making intelligent packaging a very worthwhile investment. Add this to the other advantages of less temperature excursions, more efficiency in the supply chain, and a single qualified solution to distribute to multi-sites, and it becomes clear that intelligent temperature-controlled packaging could feasibly be one of the most attractive and cost-saving technologies around.

David Johnson works as a Business Development Manager for SCA Cool Logistics focusing on the Clinical Trials market. A qualified Mechanical Engineer, David began his career working for a Pharmaceutical Process Engineering firm serving the oral solid dosage pharma markets. Working with Big Pharma, David provided process knowledge and technologies used in the manufacture of OSD products from pilot scale through to full commercial production including continuous processing. Having joined SCA Cool Logistics back in 2010 David has experienced success through being able to adapt quickly and effectively to the changing market conditions providing the right solution for the right study.
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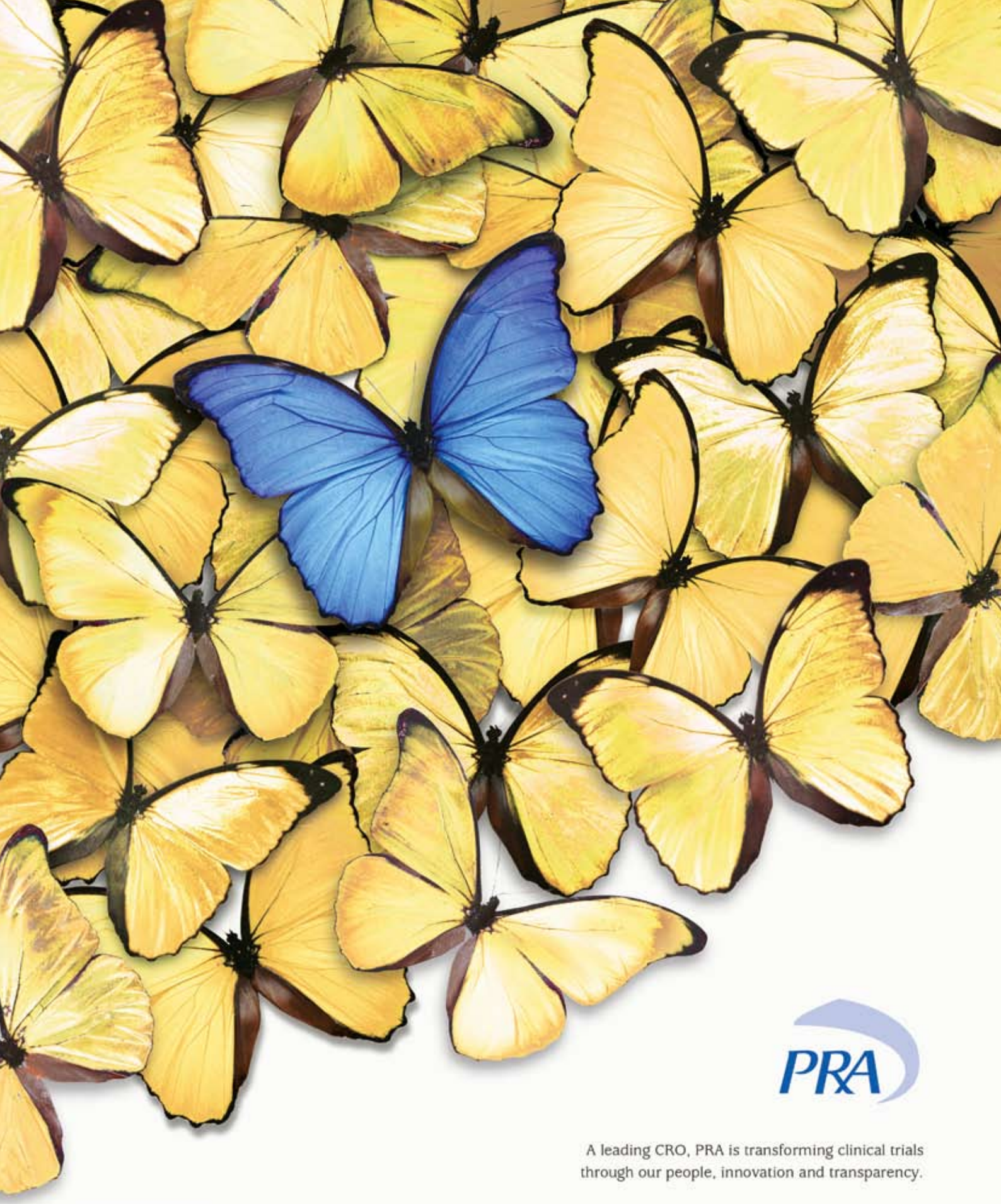

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A Clear Difference

Transforming SAE Life-cycle Management in Clinical Trials – Enabling a Streamlined Business Process through Electronic Systems

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Introduction

The process for managing Serious Adverse Event (SAE) reports within clinical trials entailed paper-/fax-based reporting of SAEs, subsequent cycles of paper-/fax-based communication of queries and responses, and manual reconciliation of key data elements to ensure alignment between clinical trial and safety regulatory reporting streams. With the goal of streamlining these processes, in 2009 Amgen embarked on implementing a "best in class", fully electronic SAE life-cycle management platform between our clinical trials database (CTDB) and safety system. At the outset of this effort, key stakeholders from Safety, Clinical Data Management (CDM), Clinical Study Management, and Information Systems (IS) outlined the following key objectives:

- Eliminate manual data reconciliation between the CTDB and safety database
- Significantly reduce the number of manual safety queries and subsequent follow-up cycles
- Optimise safety case processing productivity
- Enhance risk management through improved data quality, standardisation, and synchronicity
- Significantly reduce duplicate data entry, both at the investigator site and sponsor company

Characteristics of a Streamlined Process

In 2009, Amgen's previous technology investments and business relationships provided the proper environment for capitalising on this effort. Amgen had established an electronic data capture (EDC) system (a fully electronic CTDB) as its primary CTDB with many years of practical experience, and had already set the strategy for solely utilising this platform for all clinical trials. Vendor commitment was also a crucial component to the viability of this effort. But perhaps the most important component was the cross-functional, executive sponsorship established at the inception, coupled with talented, committed professionals in key positions who set the vision and drove the change.

While leveraging technology and standards was at the heart of our strategy, it was very evident that if we were to meet our objectives, transformational process changes must accompany technological enhancements. At a basic level, the concepts were logical. Since over 90 % of data required or meaningful for safety reporting (e.g. SAE, subject, investigation product, medical history, concomitant medications) is captured in the EDC, the strategy entailed extending the adverse event (AE) clinical report form (CRF) to include the additional safety information, package the safety case into E2B (the ICH standard for AE data structure – used to transfer SAE data to regulatory agencies and between companies), and transmit this highly structured data to the safety system. This alone offers significant improvement when compared to a paper-based process. However, when evaluating the SAE life-cycle management process comprehensively, we determined that the following process enhancements would greatly increase the value of this effort:

- Ensure a single, streamlined data entry process (coined eSAE) - critical for site compliance
  - o Leverage the CTDB as the comprehensive source by mapping all applicable safety data
  - o Apply basic data requirements (i.e. minimum data completeness) at the source by systematically ensuring required data is entered prior to transmission
  - o Enable a single, fully electronic process for transitioned studies (studies which started in a paper-based process)
- Ensure all "reconcilable fields" are entered in the EDC and are treated as read-only in the safety system (process-driven synchronisation of reconcilable fields)
- Automate the generation of medically significant safety queries for pre-specified events of interest in the CTDB prior to initial transmission
- Centralise query management by providing safety the ability to query the study sites directly in the CTDB
- Link cases between systems so that follow-up cases will be automatically recognized by the safety system

How Technology Supported the Streamlined Process

Ensure a single, streamlined data entry process – critical for site compliance

Amgen worked closely with a vendor to ensure the tool was equipped with features which enable maximum leverage of clinical data. Firstly, the system provides the capability of mapping various CRF data to E2B tags on a per-study basis. The system manages the hierarchical structure of the E2B standard, allowing for the assignment of a CRF to an E2B node (e.g. adverse event) and also allows for

the mapping of multiple CRFs into an E2B node when applicable (e.g. surgical history and radiotherapy history CRFs mapped to medical history in E2B). Secondly, the system provides a translation layer for E2B dictionary terms. This configuration can be used to meet E2B specifications for code lists (e.g. dose units, route of administration) without altering CRF configurations and data management standards (i.e. addition of non-E2B data fields). Lastly, the system provides additional mapping flexibility by enabling extension of the E2B standard. Because of this, we were able to map concepts such as event level seriousness criteria and patient race, which are not currently supported by the E2B standard.

Complementing the data mapping was a substantial effort to build systematic, real-time communication with sites through the EDC. It was recognised early on that driving a fundamental process change across thousands of sites globally is a significant challenge. In combination with an aggressive, comprehensive training strategy, our focus for the eCRF design was to be simple, in-line with established data entry practices, and to provide instructive feedback to sites in real time when required. Through a series of new edit checks and custom functions (programs that run at the time of page save), we used the EDC's querying mechanism to fulfill the following requirements:

- Inform site when SAE transmission is necessary for both initial and follow-up scenarios
- Prohibit transmission of SAE if required fields are not entered
- Raise queries to inform the site which data needs to be entered to fulfill transmission requirements
- Close queries when site performs requested actions
- Enforce various data integrity rules (e.g. ensure a serious criterion is entered only when event is serious)

Eliminating Manual Reconciliation

A key objective of this effort was the elimination of the resource-intensive, manual reconciliation process between CTDB and safety systems. At Amgen, this process entails ensuring alignment of the following key attributes: event seriousness, causality to investigational product (IP), MedDRA-coded event term (at times conceptually in absence of exact match), and patient death flag. In the eSAE process, our strategy entailed ensuring all these fields were entered in the CTDB then treated as read-only in the safety system. For the MedDRA-coded event term, this was a fundamental process change. In the paper process, event terms were coded in batches by the medical coding organization, typically after the corresponding event in the safety system was coded real-time (report by report) by the safety function to meet regulatory reporting timelines. By performing the coding process up front into the initial data entry process, this would ensure process-driven synchronisation and consistency of all fields that were previously reconciled

manually. While the medical coding organisation was amenable in theory to this solution, we were concerned that the operational impact to the change meant not only an increased workload for this function, but also a fundamental shift from a scheduled batch process to an individual event coding paradigm each with its own regulatory reporting timeline. In order to help mitigate this potential resource impact, we devised a two-pronged approach for ensuring up-front coding.

The first prong entailed leveraging the site data entry process. The verbatim term entry field was transformed to a type-forward control (e.g. like Google™) backed with MedDRA low-level terms. This provides the site user the ability to select a term from the list if the user chooses and, like Google™, the user can choose to type anything into the control. This increases data quality (i.e. correct spelling of medical terms) and efficiency (medical terms can be very long) for site staff while providing flexibility to enter the exact term of choice. When the site selects from the list, the term will "self-encode". However, if the site does not select from the list, the medical coding team is notified and codes the term prior to transmission (the second prong). In order to streamline this operation, the vendor delivered functionality called "deep-linking" which is a URL taking a user directly to the specified CRF within the CTDB for action (after user authentication). Using this functionality, the system notifies the medical coding team via email including this deep link. The medical coding team enters the CTDB through the deep link and codes the term within a short amount of time to ensure timely reporting.

Another process enhancement achieved during this effort was the standardisation of capturing SAEs observed while study subjects undergo screening procedures before receiving an investigational medical product in the CTDB. Since regulatory agencies have recently increased focus on screening procedures, our study design lead recognised the opportunity to implement a single, standard process for capturing this information. However, the infrastructure enhancements required to support this process were far from trivial. Firstly, the standard matrix was updated not only to include a screening SAE form, but also enhanced to include supporting CRFs such as Medical History. Once a subject successfully completes screening, the CRF structure is adjusted to support the standard on-study configuration. Lastly, the Integrated Voice Recognition System (IVRS) process was enhanced to transfer subject information at the time of informed consent, as opposed to the previous process of an aggregate transfer at the completion of screening.

Other system functionality designed to facilitate a self-synchronising process include case-linking between systems, enabling systematic follow-up recognition as well as the centralisation of query management in the CTDB which, will be described in more detail below.

Q & A – Electrified and Optimised

Perhaps the most daunting task in enabling a fully electronic SAE life-cycle management process was handling the query and follow-up cycle. Fortunately, the building blocks were in place to achieve this objective. Firstly (and perhaps obviously), we were able to leverage the built-in query management module of the CTDB. Couple this with the aforementioned deep link and ability to extend the E2B standard, and voila – you have a recipe for success. The basic strategy entails:

- Safety staff identifying the need to raise a query (in the safety system)
- Safety staff efficiently entering the CTDB and raising the query
- The site answers the query by changing CRF data
- The site transmits the follow-up
- Safety staff analyse the result, and close the query (or requery as needed)

The infrastructure used to support this process is as follows:

- A deep link to the AE CRF was embedded into an extension tag within the E2B file
- Once the case was transferred, the safety system exposed the deep link as an active URL
- Safety staff member enters the CTDB, raises query on appropriate CRF field
- Site staff member answers query
- The site submits follow-up
- Safety staff utilise the CTDB query governance tools (e.g. query task list, query details report) to identify answered queries, and closes query in the CTDB

An added benefit to this process enhancement was that it enabled greater transparency to raised queries cross-functionally. Through centralisation of query management in the CTDB, it is projected that there will be a significant reduction in query duplication.

Events of interest refer to pre-specified medical concepts that require enhanced surveillance. Our Medical Safety Review Team led a comprehensive, cross-functional effort to standardise the collection of medically relevant information for events of interest. This effort yielded standard query events (SQEs) – a standard set of queries associated to a medical concept. In the paper world, once an event of interest is recognised (after event coding), the SQEs are then faxed to the site which by definition is a process which builds in one or more follow-up cycles. The eSAE process, with in-process event coding, provides a unique opportunity to generate SQEs during initial data entry, providing sites the opportunity to address queries before initial transmission, reducing follow-up cycles. A combination of custom function and SQE to LLT mapping tables was provided by the vendor to enable this functionality.

The combination of SQEs coupled with enforcing data entry requirements in the CTDB (approximately a quarter of queries raised in the paper process are due to missing or unreadable data) is the cornerstone of our strategy for significantly reducing manual queries and subsequent follow-up cycles.

A Technological Spin on "Trust but Verify"

Automation is great…when it works. One challenge to introducing this level of automation is the reduction of the paper trail and corresponding manual touchpoints which, in a sense, provides built-in manual oversight. Electronic efficiency by definition reduces the tangibility of a paper process. Recognising this, the team developed the PROACT active notification system. Because the eSAE process is self-synchronising, it allows PROACT to independently compare data across systems and raise any discrepancies accordingly. When data are discrepant beyond a defined timeframe, PROACT raises the alert by sending a detailed email to the appropriate stakeholders to remediate said discrepancy. As long as the eSAE processes are followed, PROACT will not yield any results. However, it provides the ultimate safety net which is essential for instilling confidence in the self-synchronising process across the enterprise and managing the few manual decision points within the process where discrepancies may arise. PROACT provides active monitoring and alerting for the following scenarios:

- Raise alert to safety if reconcilable fields are changed in the safety system
- Raise alert to site if an SAE is entered, but not transmitted to safety in allotted amount of time
- Raise alert to site if reconcilable field(s) is (are) altered, but not transmitted to safety in allotted amount of time
- Raise alert to medical coding if coding does not occur within timeframe of internal service level agreement (SLA)
- Raise alert to safety if event is found in the safety system, but not in the CTDB
- Raise alert to safety if event has been transmitted from the CTDB, but not yet incorporated into safety system (e.g. follow-up event with "reconcilable" field change not yet accepted and incorporated)
- Raise alert to safety if two cases for the same subject with the same event term occur within 30 days (as the second may be considered a duplicate)

Taking the "Standards" Approach

Process efficiency is not limited to the business process the system supports, but also applies to the operations of the system itself. eSAE has introduced a significant increase in infrastructure including the CRF to E2B mapping module, as well as myriad edit checks and custom functions. A single variation in a field OID could potentially have a large ripple effect, requiring code changes and validation of mapping and within edit checks and custom functions. And since this infrastructure must be equipped with each study start-up cycle, managing study design variability was paramount to ensuring operational viability (i.e. not exploding current study start-up timelines).

The approach was to deliver a common set of CRFs and mappings consistent across all studies. While studies obviously have inherent differences (i.e. investigation products (IPs), varying medical history forms), the goal was to lock down as much as possible (target 80%) which includes all edit check/custom function impact. Therefore, the only study-specific operational impact would be mapping the remaining 20%. Furthermore, as we gain more experience, we project supplemental standards for a given therapeutic area (TA) or IP can be achieved, thus providing a greater reduction in study-specific variability. Amgen has further demonstrated its recognition of the value of standardisation by aggressively engaging in a Clinical Data Interchange Standards Consortium- (CDISC-) based initiative, and the two project teams have worked closely to ensure seamless integration.

Implementing Transformational Change – Iterating Iteratively

Delivering transformational change for such a fundamental, established process required a total team effort. Our operational team was comprised of leaders from a broad spectrum of functions including safety (case management and medical review), clinical data management, CRA liaisons, development operations, biostatistics, clinical quality assurance, training, and IS. With such a large, cross-functional team, consistent communication was critical for realising and refining requirements and ensuring alignment. While iterative development is fairly standard in software development today, the ability to incrementally course-correct was paramount to successfully establishing the new process. The validation plan was comprehensive, including three rounds of integration testing prior to operational qualification (OQ). The strategy also entailed soliciting feedback from all key stakeholders as early as possible, then consistently throughout development including both internal functions as well as external study site staff. Roadshows with mock-ups and prototypes evolved into working sessions within an active development environment. Additionally this strategy delivered major dividends in uncovering requirements that were previously unrecognised. As an example, the need to build a form-based report to send to investigational review boards (IRBs) was realised during a pre-release visit to a site who volunteered to provide feedback. Early engagement enabled the team to address key gaps well before real-world impact.

To our benefit, the iterative approach was a shared philosophy between Amgen and our vendor. Even though there was an eight-hour time difference, the teams worked diligently to maintain communication through countless cycles of requirements-gathering and refinement, development, informal user acceptance test (UAT), and formal validation. Maintaining a high degree of verbal communication between analysts and developers was critical, as it not only ensured in-depth alignment between requirements and design (and ultimately the end product), but it also facilitated vital discussion concerning the use of technology (and sometimes its constraints) to practically meet business needs leading to much of the functionality described above.

The iterative approach was not simply limited to the development cycle. Our implementation approach entailed transitioning twelve diverse studies into production, then evaluating and adjusting before ultimately releasing on an enterprise basis, including all new studies and additional active study transition (i.e. a pilot). This decision truly demonstrated our commitment to the iterative approach as transitioning active studies comes at a comparatively high cost in relation to new study implementation. Firstly, transitioning a study meant applying eSAE infrastructure (mapping, edit checks, custom functions) to established CRFs, which based on their creation adhered to different standards. Secondly, in order to enable a fully electronic process, the team migrated safety-specific SAE data into the CTDB for legacy cases. Lastly, the training and change management component requirements for facilitating a fundamental process and behavioural change on global studies were an immense undertaking. For the twelve "pilot" studies, training was developed and successfully delivered to site staff, CRAs, and functional staff (e.g. safety case management, data managers, etc.) in 35 countries and over 500 sites.

Although the effort was significant, the approach yielded invaluable feedback. Six weeks after the release, sites participated in a survey which provided positive and constructive, actionable feedback as well. During this "hypercare" period, the team was able to make adjustments to both the technology and processes. But equally as important, it afforded us the opportunity to engage in the change management aspects evaluating the success of our training, support infrastructure, and overall site compliance to the new processes.

The Results

Within the first three months having the twelve studies transitioned in production, the system facilitated nearly 1300 transactions equating to approximately 700 distinct SAE cases from 35 different countries. After ten months, the cumulative number of transactions has grown to over 4500. After receiving approval from the senior management to equip all new studies with eSAE (with rare exemptions), the team has successfully implemented the first of many new studies in September of 2011. Furthermore, the team has embarked upon a second wave of high priority transition studies. The core team has primarily remained intact, fostering the transition of responsibility to operational functions concerning the alignment of study start-up activities for safety and CDM. Functional champions have established operational forums to manage change and discuss future strategy. With the combination of new study implementations and transitioned studies, it can be projected that over 90 % of Amgen's study portfolio will be eSAE-enabled by the end of 2012.

With regard to our goals and objectives, while some were qualitative objectives and others were boolean (e.g. did we eliminate manual reconciliation? – which we have, consistent with process adherence), reducing the number of manual queries is a quantifiable measure which can be

tracked. Overall, investigators have received 39 % fewer queries on an eSAE study when compared to a paper study. Furthermore, of the queries received by investigators on eSAE studies, 30 % of these were system auto-generated SQEs. Therefore in total, safety is manually posting 57 % fewer queries in eSAE in comparison to paper studies, which exceeded our expectation.

While we at Amgen are very excited about the value that eSAE has provided and will continue to provide, there certainly were a number of noteworthy challenges the team was and is required to overcome. While this in itself could be a separate publication, listed below are some of the most significant.

- **Study transitioning** – while strategic study transitioning has increased our ability to remove paper studies and manual reconciliation processes by approximately six years, it was a meticulous, resource-intensive effort which required an extreme level of coordination across multiple functions
- **Ensuring operational efficiency while increasing infrastructure** – there is an inherent upfront cost to incorporate eSAE into existing study start-up timelines, given the increased infrastructure and configuration. To minimise this cost and ensure that study start-up timelines are not negatively impacted, the team has increased focus on standardisation (i.e. reuse of standard CRFs and mapping), aggressive training on new applications and tools to all appropriate staff, and clear functional governance of eSAE components as well as cross-functional impact awareness.
- **Managing study variation** – most supporting this industry can attest that no two studies are the same. However, some study types have required significant

analysis on how best to handle (or potentially not handle) within the eSAE process.
  - o Observational studies – managing the difference in the sponsor's safety reporting responsibilities in contrast to clinical trials
  - o Roll-over studies – oftentimes, elements needed by safety (e.g. medical history) are not included
  - o First-in-human (FIH) and early development studies – given that SAEs are often rarely reported, there is a significant question concerning cost-benefit for these studies
- **Managing change while changing** - even though we have greatly increased our overall transition timeline through the efforts outlined above, Amgen still must actively manage multiple processes (eSAE and paper) for a couple of years. This is most challenging to central functions such as safety who work across studies, molecules, and even therapeutic areas. Some of the practical challenges include:
  - o Developing and maintaining two distinct operational processes including documentation, training, etc. regarding safety case management
  - o Ensuring efficient identification within the safety system of which process to adhere to
  - o For eSAE, globally aligning all stakeholders, including business partners, to a single process
  - o Working out the details – a big challenge to a first-in-industry paradigm is that there are not any reference points or resources with experience. An example where the team has had to provide specific focus is driving the paradigm shift where specific eCRFs within the CTDB are actually the "source document" for the safety case.
- **More tightly coupling processes between safety, CDM, and development** – while the eSAE process offers significant efficiencies, it also requires greater alignment between functions and in a few cases, blurs lines of accountability. Below are a few examples:
  - o Aligning data conventions between CDM and safety (especially concerning event capture conventions)
  - o Providing safety staff appropriate level of training for querying in CTDB and leveraging CDM query conventions
  - o Clearly outlining ownership, responsibility, and cross-functional interaction for governing safety queries in the CTDB
  - o Providing cross-functional, systematic communication/escalation channels between safety, CDM, and development.

In today's environment, streamlining core operations may be more important than ever to ensure we can deliver vital, novel therapies to patients throughout the world. At Amgen, the eSAE initiative represents a big step in the right direction. The approach of process-focused system delivery coupled with consistent, iterative communication with a broad set of stakeholders has enabled us to deliver an innovative solution which enables Amgen to manage the SAE life-cycle responsibly - not only significantly increasing efficiency, but also improving quality and availability of this critical information. And ultimately, it is the patients we serve who will reap the benefits of what we have learned for many years to come.

Marty Markley has over fifteen years experience delivering innovative solutions across various functions supporting drug discovery, development, and life science industries. While at Amgen, Marty has led efforts to improve efficiency, data quality and standardisation, and decision-making capabilities within clinical and post-market drug safety, clinical data management, risk evaluation and mitigation strategy (REMS), analytical chemistry, and drug discovery. He can be reached at **Email: mmarkley@amgen.com**

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Enhancing Late Phase PRO Collection with Mobile Technology

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Introduction

Patient-reported outcomes (PRO) are increasingly being recognised as a key source of data on the safety and efficacy of new medical treatments. Driven by the growing emphasis on the patient perspective in healthcare, PROs measure the effect of a medical intervention on a patient's health condition as reported directly by the patient, without interpretation by a clinician or anyone else. Treatment impact can be assessed most accurately through the use of PRO measures, which are defined as: any assessment resulting from patients' self-reports, collected through tools such as event logs, symptom reports or longer questionnaires. Recent Food and Drug Administration (FDA) (and European Medicines Agency (EMA)) guidelines stress the importance of PRO, stating that findings which are measured by a well-defined and reliable PRO instrument can be used to support a claim in medical product labelling.

The collection of accurate and real-time PRO data is of increasing importance in late phase (post-approval) research, where the focus is on monitoring product safety and establishing the clinical and commercial benefit of a drug in the "real world". Late phase research also aims to support labelling and marketing claims, local requirements, health economics data and market readiness. PRO plays a key role in providing the data to ensure these goals can be realised, ultimately ensuring the successful support of safe and effective drugs, in compliance with current legislation.

The Challenge of 'Real World' Data Collection

Pre-registration studies include PRO to evaluate a compound's safety and efficacy in a relatively small group of patients, within a controlled (test) environment. In contrast, late phase trials are multi-purpose and collect more safety-specific PRO data from a much larger and broadly diversified patient population over a longer and often undefined duration. Data are collected in a real-life setting with minimal 'touch points' from the data collector, requiring following patients through their normal course of treatment to enable better determination of the factors leading to treatment impact.

The long and undefined duration of late phase studies, together with the fact that these trials involve minimal intervention, often result in poor patient engagement and low rates of compliance, thus leading to the collection of inaccurate and incomplete PRO data. Additionally, the large scale and timeframe of late stage research usually results in low levels of technology adoption for the collection of PRO data, due to the associated hardware costs and complex logistics. This is compounded by the smaller budgets that are typical of late phase trials, in comparison to the much larger budgets allocated for pre-registration studies. The broad patient diversity and real-life setting of late phase studies also make it a challenge for sponsors to find and implement a PRO model that is flexible and accessible enough to be customised for use in individual participants' lives.

The Advent of Mobile PRO Collection Technology

The collection of PRO using electronic means is now being recommended by industry regulators. In 2010 the FDA released a Draft Industry Guidance on Electronic Source Documentation for Clinical Investigations which recommends the use of electronic means of data capture over paper, in order to ensure quality, reliability and traceability. The document also sets standards for tracking and movement of data across systems.

A key method of electronic data capture is through the use of a mobile phone, a technology which is globally recognised as the most ubiquitous communication tool. Recent research data demonstrate that 84% of the world's population owns a mobile phone, with the total worldwide number recorded as 5.9bn in 2011. This number represents more than four times the number of landline phones (1.2bn) and three times the number of internet connections (2.1bn). In line with the increasing presence of mobile technology, new technological advancements have seen the introduction of advanced mobile phone-based solutions for use in clinical trials and healthcare programmes. These solutions create a simple and effective data collection interface for participants globally, enjoying unrivalled adoption in the patient population whilst enhancing compliance and retention rates.

Mobile-based ePRO offers the pharmaceutical and healthcare industries a real-time, easy-to-use data capture solution which can be customised to suit the requirements of the trial. The user interface is familiar and offers an intuitive design to provide easy navigation that enhances the user experience; this positively impacts patient adoption and ongoing compliance, regardless of age and demographics. Where specific and targeted data collection is required, patients can complete questionnaires via a series of text messages sent intermittently to their own mobile phone. If a response is not received by the patient within a certain timeframe, a text message reminder can be automatically sent in order to prompt a response. This is extremely valuable for late phase trials running over long timeframes, ensuring that participants remain motivated and compliant, no matter what the length of time between visits or surveys. In addition, the ability to capture patient data in "real time" means that investigator site staff can be alerted to abnormal patient data and react accordingly to ensure patient safety.

Where more complex patient data or lengthier responses are required, eDiaries can be deployed. Patients

receive a text message which contains a link to a secure mobile internet site containing the eDiary. The patient then connects via the mobile internet URL and enters their unique PIN to access the ePRO questionnaire. This type of technology enables a wide range of questions to be presented and viewed on most cell phones. (In cases where the user's own phone is not able to access the internet, backup phones can be made available.) In addition, questionnaires can be customised to improve ease-of-use for the patient by including widgets such as radio buttons and check boxes. Real-time reporting can also be easily built into the system, which enables the sponsor to view eDiary responses as they are submitted, and respond quickly to any issues.

The accessible and easy-to-use nature of mobile technology provides a highly patient-centric approach, enabling patient data capture as close as possible to the point of experience. The simplicity of the mobile technology interface also removes the problem of patient reporting being too time-consuming or onerous, therefore enhancing compliance rates.

Severe Haemophilia Trial Case Study

Results from an ongoing trial into severe haemophilia indicate the benefits of mobile technology on long-term adherence. The trial involved the administration of a prophylaxis treatment which required patients to inject either every two or every three days. Due to the ad-hoc nature of the medication regimen, typical patient adherence is as low as 55 %[3], with patients often forgetting to administer the correct dose at the right time. Mobile technology was implemented in order to improve patient compliance with the medication regimen and to maximise patient diary data collection. It was also hoped that the use of mobile technology would enhance patient connectivity with healthcare practitioners, and as a result benefit consequent treatment interaction. The results of this severe haemophilia trial indicate a medication adherence rate of 95.6 %, a significant increase of 40 % on usual rates. Due to the success of these results, the initial 18-month timeframe of the trial has now been extended.

As an additional benefit, the implementation of the mobile technology allowed the healthcare practitioner (HCP) feedback loop to ensure patient safety during the trial. When one patient suffered a severe allergic reaction to the treatment, the HCP was able to use the stored data to immediately identify the affected batch and then notify other patients with the same batch number not to use those vials. This example demonstrates the capacity of mobile technology to capture and track key patient information in order to further assist HCPs in proactively managing patients and their disease.

Conclusion

As mobile technology becomes increasingly embedded into everyday life, stakeholders are recognising that leveraging existing technology, rather than investing money into new technology, is the logical and smart way of integrating efficiency and quality PRO into late phase clinical trials. With the use of mobile ePRO, late phase data can be centralised instantaneously, allowing for real-time patient progress and compliance monitoring, health tracking and reporting. As a result, this drives proactive engagement with healthcare sites and patients to ensure that all stakeholders are connected, motivated and compliant, regardless of the length of time between visits and surveys.

With the healthcare industry shifting into a new phase, based on the paradigm of electronic health records and increasingly empowered patients and personalisation, mobile technology facilitates greater control and oversight around healthcare, while also giving patients a tool to ensure their voice is heard.

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Interview feature: Journal for Clinical Studies speaks with Prism Ideas

Abstract
Patients are increasingly using the internet to share experiences of their diseases, symptoms and treatment. Opinion expressed freely within internet forums, chat rooms and social media sites can be extremely useful to understand patients' behaviours and the reason for their actions. The emphasis on the importance of patient perspective is increasing, but generic approaches to data gathering have been disappointing. However, advances in natural language-processing technology now allow the wealth of patient-reported outcomes data on the internet to be harnessed. Last month, Prism Ideas (www.prismideas.com), the multinational medical marketing and drug development consultants, teamed up with dMetrics (www.dmetrics.com), a decision engine able to search the decisions made by millions of patients online, to launch a pioneering analysis service to evaluate patient healthcare outcomes. The collaboration has already successfully completed projects in a range of disease areas from multiple sclerosis and allergic rhinitis (hay fever), to smoking cessation. *Journal for Clinical Studies* spoke to Dr James Sawyer, CEO at Prism Ideas and Paul Nemirovsky, CEO at dMetrics, to discuss the new venture.

Can you explain in more detail about the innovative patient healthcare outcomes analysis service that Prism Ideas and dMetrics have launched?
The pioneering analysis service explores internet chatter to assess patient healthcare outcomes. It combines expertise in language analytics and healthcare to interrogate the internet to determine patient actions and perceptions, and profile patient needs, symptoms and response to treatments. The service is fully compliant with industry standards of practice in both market research and pharmacovigilance, and the reports can be used for drug development planning and product assessment, and for providing information on disease epidemiology, symptoms, clinical outcomes and side-effects to treatment. In addition, the service can deliver patient insight and value judgements. This application of using online patient decisions as a research tool for the pharmaceutical industry is completely unique and demonstrates the companies' dedication to being at the forefront of innovation.

How will the use of internet chatter help to advance the evaluation of patient healthcare outcomes?
The real-time data collected from the internet will provide researchers with valuable, non-biased insight into patient needs and what outcomes patients expect from a particular therapy. From these 'real-world' data it is possible to determine patient actions in relation to treatment, as well as the sentiment and reasons underlying patients' decisions. The research mechanism is unique and provides meaningful patient insight data for healthcare providers and the pharmaceutical industry. The Prism Ideas and dMetrics offering brings an unparalleled opportunity to directly understand patients' experiences reported in their own words. In addition, the traditional labour-intensive approaches to assessing patient reports are eliminated with the use of this service, allowing for significant time and cost savings.

How does the new analysis service work and how does it differ from other systems?
Unlike simple keyword-based market research systems, dMetrics' MIT-founded decision search engine harnesses 'Big Data' to identify who makes decisions, what they decide, and why those decisions are made regarding a product. This multitude of voices is then connected into a compelling patient narrative and analysed through complex, healthcare-specific algorithms. Together, Prism Ideas and dMetrics are able to bring previously unavailable, unbiased insight and analysis of the collective action of many individual patients. The service uses fewer resources than other methods and allows researchers to directly understand patients, their needs and responses to treatments.

What benefits does the new technology offer to sponsors?
Due to increasing regulatory and healthcare provider interest in patient-reported outcomes, there is a growing need for technology that can measure and empirically substantiate the benefits to patients of new medical products. The service offers previously unavailable, unbiased insight and analysis of the collective action of many individual patients. An added benefit to sponsors is that the service can be tailored to meet their specific requirements. This means that sponsors can collect and deliver meaningful and longitudinal data without the hurdle of long lead times or regulatory committees. By using the service, researchers will be provided with improved quality data that avoids complications such as reviewer bias and subjective assessment. In addition, the technology could provide pharmaceutical companies with an effective method of capturing real-world safety information to fulfil their pharmacovigilance obligations.

Can you provide a real-world example?
Prism Ideas and dMetrics recently teamed up with Allergy Therapeutics, a speciality pharmaceutical company providing allergy vaccines, to conduct an *in silico* study to establish the level of symptom improvement considered to be meaningful by sufferers of hay fever. No prior clinical or regulatory consensus was held on this subject, yet regulators

had expressed their requirement for these data. During the study, the team captured first-person data reports relating to treatment intervention, symptoms impacted and outcomes-related sentiment. The results provided Allergy Therapeutics with key data that showed that for many patients, the relief of just one hay fever symptom, such as a blocked nose or sneezing, was very important.

Dr James Sawyer, CEO, Prism Ideas.
Following a clinical career in general medicine and anaesthetics, James moved to the pharmaceutical industry in 1993, holding leadership positions in companies including Sanofi, AstraZeneca and Roche. James's clinical development experience spans all phases of clinical research and he has published widely across a variety of therapeutic areas. He has driven regulatory interactions for many compounds and is the author of several expert reports filed at European and North American agencies. James founded Prism Ideas in 2001.
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Dr Paul Nemirovsky, CEO, dMetrics
Prior to founding dMetrics in 2009, Paul earned his doctorate at MIT, with 15 academic publications in the fields of human-computer interaction and machine learning. He has 15+ years of experience in managing development teams at startups and at MIT and has overseen and helped launch a number of successful commercial and academic projects. A professional musician in his past life, Paul's interactive work has been exhibited at Centre Pompidou, Decordova Museum, and other venues around the world.
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Central and Eastern Europe – The Right Region for Antibacterial Drug Development, with Romania as the Place of Choice

PEER REVIEWED

Introduction

Selection of countries participating in antibacterial drug development should first of all be justified by the spectrum of antibiotic resistance of the pathogens that are going to be isolated during the trials. From this standpoint, the US is the best place, since this country is the leader in antibiotic resistance of their pathogens, which is a factor of utmost concern to their healthcare professionals, but is also dictating the need to demonstrate efficacy of novel antibiotics against the local pathogens.

The globalisation of clinical trials is also taking place in antibacterial drug development, and more and more countries are becoming engaged in these studies. It is obvious, however, that the most interesting are those countries where the level of antibiotic resistance is also high.

Traditionally acute bacterial skin and skin structure infections (ABSSSI) are one of the first indications that allow the assessment of efficacy and safety of a new antibacterial drug in the most efficient way. The study design of pivotal trials in this indication is that of an active control comparative non-inferiority trial, i.e. the study drug is tested vs. the current "golden standard" of treatment. This is why key importance is attributed to proving the fact that the study drug is able to fight with "sufficiently" resistant pathogens, otherwise the data would not be convincing. For example, due to the high quality of healthcare and strict observance of sanitary standards, the Scandinavian countries shouldn't be considered the countries of choice for this type of drug development, since these countries may be proud of a very low level of antibiotic resistance.

Choosing countries for clinical trial conduct is made easier by the data of the antibiotic resistance surveillance, which is available for most developed countries. For emerging countries and regions, however, these data are not complete and this is why we have made an attempt to summarise our data received during the conduct of clinical trials.

ABSSSI are a frequent reason why patients would want to see a surgeon and also a basis for hospitalisation, surgical interference, and a reason for prescribing antibacterial medications (ABMs)[1,2,3,4,5]. Based on the data of an epidemiological study conducted in five Western European countries (UK, France, Germany, Spain, and Italy), ABSSSIs are the cause of about 1.3 million cases of hospitalisation per year (according to 2004 data)[6]. At the same time, about 25 % of the cases of hospitalisation are related to the complicated ABSSSI of nosocomial origin[6].

The major role in the etiology of ABSSSI is played by the bacterial pathogens. Separate cases could be caused by rare and/or "unusual" bacteria (*Alcaligenes* spp., *Corynebacterium* spp., *Mycobacterium* spp., etc.), and in many cases polymicrobial infections are present. In every case the likelihood of the infection caused by a certain pathogen depends on a number of factors, such as the infection source and pathway, localisation of infection, its complexity, and the presence of coexistent illnesses.

According to the traditional concept, the most common bacteria participating in the infection process in ABSSSI are usually Gram-positive aerobic bacteria (*Staphylococcus aureus, Streptococcus pyogenes* and to a smaller degree the Streptococci of groups B, C, and G, and Enterococci), Gram-negative aerobic bacteria (the representatives of the family of *Enterobacteriaceae* and *Pseudomonas aeruginosa)*, as well as anaerobic bacteria *(Bacteroides* spp., etc.)[7,8,9,10,11,12,13]. There are significant differences between the etiology of non-nosocomial and nosocomial ABSSSI: when infection has been transmitted nosocomially, resistant Gram-negative bacteria, Enterococci, and coagulase-negative Staphylococci (CNS) are isolated more frequently, while the strains of S. *aureus, Streptococcus* spp. and anaerobes are isolated in relatively fewer cases [7,8,9,10,11,12,13].

According to the opinion of the experts from the US Surgical Infection Society, the results of epidemiology studies in hospitalised patients with ABSSSI may yield data understating the etiological role of *Streptococcus pyogenes* due to the complexity of obtaining proper samples for microbiology studies in patients with streptococcal ABSSSI[14,15].

On the whole, *S. aureus* is the most common pathogen causing ABSSSI, both of nosocomial and non-nosocomial origin, amounting to 25-50 % of all isolates [57,8,9,10,11,12,13,16,17]. More recent epidemiology studies that included data on ABSSSI (both of non-nosocomial and nosocomial origin) that required hospitalisation demonstrated a relative increase of the role of *P. aeruginosa*, enterobacteria, and Enterococci in the etiology of such infections[16,17], as well as the increase in the frequency of the isolation of *S. aureus*, resistant to methicillin (MRSA)[16,18].

Infections caused by MRSA are a serious problem since they lead to the increase of mortality and treatment expenses[19]. Similarly, the presence of CNS and *Enterococcus* spp. having natural and acquired resistance to many classes of ABMs also creates difficulties when choosing appropriate antimicrobial therapy for ABSSSI. Due to the above, there are currently many ongoing studies of efficacy and safety of new ABMs active against resistant aerobic Gram-positive microorganisms in patients with ABSSSI.

Companies planning the conduct of such studies need to have an idea of the spectrum of ABSSSI pathogens in different regions ahead of time to make grounded decisions on the participation of sites from different countries in their clinical trials. Unfortunately, systematic data on the types

of ABSSSI pathogens are available only for hospitals in the US and Western Europe, which is obviously the reason why other regions are not getting more actively involved in the studies of new antibiotics.

This paper is analysing the results of the microbiological studies in hospitalised patients with ABSSSI participating in international multi-centre clinical trials (IMCCTs) of new ABMs in the treatment of infections caused by Gram-positive microorganisms, or by an association of pathogens with the prevalence of Gram-positive flora before the start of antibacterial therapy to identify the etiological pattern of ABSSSI at the investigative sites in Central and Eastern Europe (CEE).

Methods

Analysed Clinical Studies

An analysis has been performed of the joint database that included the results of microbiology studies of clinical material obtained from patients participating in five IMCCTs of new ABMs for the treatment of infections presumably caused by Gram-positive microorganisms in 2007-2009, suffering from ABSSSI and hospitalised immediately before a microbiology assay. 56 investigative sites located in Russia (14 sites), Latvia (10 sites), Poland (nine sites), Romania (eight sites), Ukraine (eight sites), and Lithuania (seven sites) have participated in these microbiology studies.

All studies have been conducted according to the guidelines of the US Food and Drug Administration for the studies of medications for treatment of ABSSSI[20]. According to the FDA definition, ABSSSI are infections affecting deep structures of soft tissues and requiring significant surgical intervention and/or ABSSSI in the presence of coexisting medical conditions or conditions complicating the achievement of adequate treatment response[20]. However, the protocols of the analysed IMCCTs did not include patients with a number of ABSSSI types that presented the most serious difficulties for treatment.

The main inclusion criteria for patients were the following: 1) aged ≥ 18 years old; 2) signed informed consent form to participate in the study; 3) hospitalisation due to ABSSSI (e.g. infected ulcers; burns of I-II degree occupying at least 20% of the body surface; significant abscesses; advanced (≥ 10cm^2) or deep cellulitis; infected wounds); 4) presence of local symptoms of ABSSSI (purulent discharge, or at least three symptoms: discharge from the wound, erythema of ≥ 1cm from the edge of the wound, edema and/or induration, local hyperthermia, pain or tenderness to palpation; 5) the presence of at least one general symptom of infection (fever >38°, leucocytosis >10•10^9/l or >15% of immature neutrophil forms); 6) the possibility to collect material for a microbiological study.

Patients with the following types of infections were not enrolled into the studies: non-complicated ABSSSI; ABSSSI not requiring the administration of ABMs; ABSSSI caused by viral, fungal pathogens or parasites; infected bite wounds; infected bedsores; infections accompanied by the syndrome of diabetic foot or significant damage of blood circulation of a limb with high probability of amputation; necrotising fasciitis or gangrene; infections related to prosthetic devices or implants; suspected or confirmed osteomyelitis.

Patients with coexisting illnesses requiring the administration of systemic aABMs were not eligible to participate in the study, as well as patients with different immunodeficient conditions (HIV infection, neutropenia, etc.), complicated coexisting kidney, liver, cardiovascular, hematogenic, nervous, endocrine, electrolyte balance pathologies, cancer, and known hypersensitivity to investigated ABMs. Pregnant or lactating women, as well as patients who did not use effective contraception, did not participate in the study.

Patients receiving concomitant therapy with high-dose glucocorticosteroids or drugs able to react with investigated ABMs were not enrolled in the study.

It is important to note that patients who had received therapy with systemic ABMs potentially active against Gram-positive microorganisms seven days prior to enrolment in the study did not participate in the study with the exception of cases of confirmed ineffectiveness of the therapy or confirmed resistance of the isolated pathogen to the administered ABM in the absence of resistance to investigational drugs.

The main microbiological criterion for the enrolment of patients into the study was the detection of prevalently Gram-positive microorganisms during a microscopic assessment of a Gram-stained smear of clinical material obtained from an infection site at an investigative centre. Enrolment of patients with mixed infections (Gram-negative and/or anaerobic bacteria) was allowed, but only in cases when, in the investigator's opinion, the main etiological agent of ABSSSI was a Gram-positive pathogen. This way, in all analysed IMCCTs, there was a target selection of ABSSSI caused by Gram-positive microorganisms.

Procedure for a Microbiology Study of Clinical Material

At the screening visit, clinical material from the infection site was obtained from all patients to perform a microbiological study (mandatory enrolment criterion). The following types of clinical material were considered acceptable for microbiology studies in patients with ABSSSI: tissue biopsy samples, pus or aspirate obtained from the infection site. Collected clinical material was placed in the Port-A-Cul (BBL, USA) transport system and subsequently shipped in thermo-stabilised conditions to a regional microbiology lab for further examination.

In regional microbiology labs, a standard microbiology study of the collected samples of clinical material was performed following a uniform protocol and targeted at the isolation of aerobic and anaerobic microorganisms. The identification of isolated microorganisms was carried out to detect the genus and type in accordance with the capacities and standard procedures accepted in the regional laboratories. Eventually, all microorganisms viewed by the investigators as clinically significant in ABSSSI were shipped to the central laboratory, where re-identification and detection of sensitivity to ABMs were performed.

The collected data were entered into the joint database containing the main information on the results of the

microbiological study of unique isolates obtained at the IMCCT screening visit from clinical material of hospitalised patients with ABSSSI presumably caused by Gram-positive microorganisms. Thus, the database contains the information on the original microbiology landscape in ITT population.

Methods of Statistical Analysis

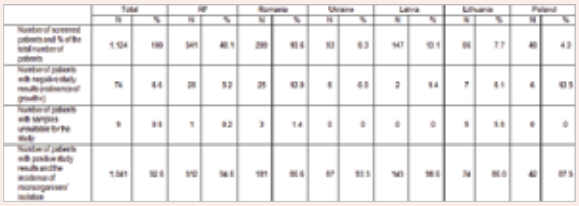
The evaluation of matching parameters of binominal distribution using Laplace approximation was applied when checking the statistical importance of the differences in the incidence of microorganisms in the regions where investigation was conducted.

Results

Demographical Characteristics and Nosology

On the whole, in 56 investigative sites the screening samples were obtained from 1124 patients. The majority of patients (541, i.e. 48.1 % of the total number of patients) were screened in the Russian Federation, 209 patients (18.6 %) in Romania, and 147 (13.1 %) in Latvia. In Ukraine, Lithuania, and Poland there were 93 (8.3 %), 86 (7.7 %), and 48 (4.3 %) patients screened correspondingly (Table 1).

Table 1. General data of the microbiology study results in patients with ABSSSI participating in the analysed IMCCTs



Samples from only nine patients (0.8 %) turned out unsuitable for a microbiology assay (delivered to the regional lab 48 hours after the material was collected) which is proof of the proper organisation of the logistics part of the studies.

Results of microbiological studies turned out negative (absence of microorganisms' growth) for 74 out of 1,124 patients (6.6 %). The majority of negative results of a microbiological study was demonstrated in Romania (25 out of 209 patients, i.e. 12.0 %) and in Poland (six out of 48 patients, i.e. 12.5 %), while the majority of the unsuitable samples was recorded in Lithuania (five out of 86, i.e. 5.8 %). The frequency of the isolation of microorganisms in ABSSSI averaged 92.6 % (86 %-98.6 % in different countries) (Table 1).

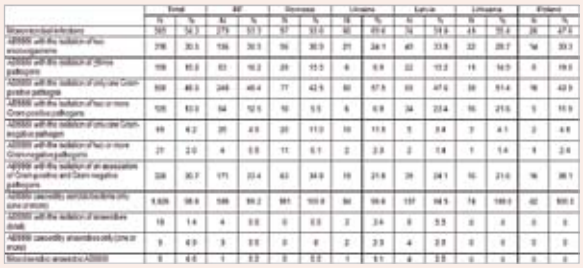
In total, 1723 unique isolates of microorganisms were obtained from 1041 patients (an average of 1.7 microorganisms per patient). This way, in many cases ABSSSI had polymicrobial etiology. In fact, monomicrobial infection was diagnosed in a little more than half the patients with positive results of the microbiological study (in 565 out of 1041, i.e. 54.3 % of the patients). 318 patients (30.5 %) had two microorganisms isolated, and in 15.2 % of cases three or more pathogens were detected (Table 2). The associations of Gram-positive pathogens with Gram-negative bacteria were observed in 30.7 % of the patients, while the associations with anaerobic microorganisms were observed in 0.6 % of the patients (Table 2).

Regardless of the fact that the goal of the analysed IMCCTs was the inclusion of patients with ABSSSI caused by Gram-positive bacteria, a number of patients had only Gram-negative microorganisms (6.2 % in monoculture, 2 % in association of two or more Gram-negative bacteria), or only anaerobic microorganisms (in 0.9 % of cases) isolated.

On the whole, only 178 out of 1124 screened patients (15.8 %) were found not eligible for further microbiology studies (as part of the IMCCTs) of clinical material obtained at the screening visit (negative results, unsuitable samples or the absence of Gram-positive microorganisms' growth), even though they were eligible to be enrolled in the studies according to the inclusion/exclusion criteria.

Most frequently anaerobic microorganisms were isolated in the regional microbiology labs in Latvia (5.5 %) and Ukraine (3.4 %). In Romania, Lithuania, and Poland no strains of anaerobic bacteria were isolated (Table 2). Generally, anaerobic bacteria were only isolated infrequently (1.4 % of the patients).

Table 2. Incidence of monomicrobial and polymicrobial infections in patients with ABSSSI participating in the analysed IMCCTs



Considering the significant prevalence of ABSSSI caused by the association of Gram-positive and Gram-negative microorganisms (30.7 %), it was not possible to identify credible differences in the incidence of this condition in different countries: the obtained results were 21.6-38.1 % of cases.

The data on the prevalence of different types of microorganisms isolated in hospitalised patients with ABSSSI in the analysed IMCCTs are presented in Table 3.

Based on the results of the studies, the most frequent pathogen causing ABSSSI in the analysed patient population is *S. aureus*, which was isolated in 66.2 % of the patients (59.5-70.7 % in different countries). It is conspicuous that there is almost equal frequency of the isolation of this microorganism as monoculture (generally 49.8 %) and in associations (50.2 %). Moreover, this ratio, on the whole, is characteristic for all countries that participated in the IMCCTs, except Ukraine, where the incidence of the isolation of *S. aureus* in monoculture was significantly higher (71.2 %) than in associations (28.8 %) (Table 3).

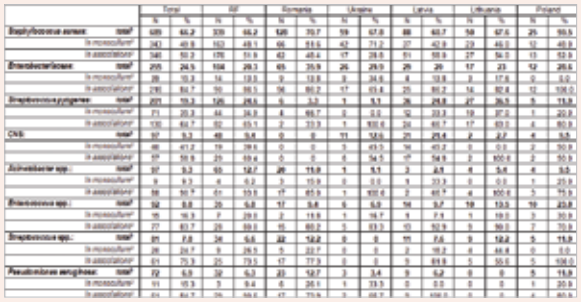
Regardless of the fact that the analysed IMCCTs were focused on the study of new ABMs to treat ABSSSI presumably caused by Gram-positive bacteria, the second most frequent isolates in the patients of this population were the representatives of the family *Enterobacteriaceae*

Table 3. Incidence of the main bacterial pathogens of ABSSSI in patients participating in the analysed IMCCTs

Note:

1 total number of the isolated cultures and the % of patients that had this microorganism isolated

2 number of isolated cultures and the % of the number of isolates of this type



(Table 3). Different types of enterobacteria were isolated in 255 patients (24.5 %), while the incidence of their isolation varied from 20 % and 20.3 % in Latvia and the Russian Federation respectively to 35.9 % in Romania. Considering that the analysed IMCCTs could only enroll patients with ABSSSI that had mostly Gram-positive bacteria detected during a microscopic assessment of a Gram-stained smear, in the majority of cases enterobacteria were isolated as part of the associations with Gram-positive microorganisms. In monoculture they were isolated mainly only in 15.3 % of the patients, with the variations in different countries from 0 % in Poland and 13-14 % in the Russian Federation, Romania, Ukraine, and Latvia, to 17.6 % in Lithuania (Table 3).

As expected, *S. pyogenes* occupied the second place among Gram-positive pathogens of ABSSSI (and the third-ranking place on the whole). Group A beta-hemolytical streptococcus (GABHS) was isolated in a total of 201 patients with ABSSSI (19.3 %). However, significant differences in the incidence of isolation of this pathogen in different countries have been identified: from single isolates in Ukraine and Romania to 25 % in the Russian Federation and in Latvia, and 36.5 % in Lithuania. In the countries with high incidence of GABHS, this microorganism was isolated as part of the associations in about two-thirds of cases, and only in one-third of cases as monoculture (the ratio in all the countries: 64.7 % and 35.3 % respectively) (Table 3).

The following types of microorganisms were isolated in patients with ABSSSI more than twice less frequently than S. pyogenes and seven times less frequently than *S. aureus*: CNS (in 97 patients, i.e. 9.3 %), *Enterococcus* spp. (in 92 patients, i.e. 8.8 %) and *Streptococcus* spp. (in 81 patients, i.e. 7.8 %). All specified microorganisms were assessed by the investigators as having clinical significance in the etiology of ABSSSI in the respective patient population.

The frequency of CNS isolation significantly varied depending on the country. For example, in Romania and in the majority of cases in Lithuania, CNS were not considered to be etiological agents of ABSSSI, while in the Russian Federation, Ukraine, and Poland they were considered significant pathogens in about 10 % of the patients, and in Latvia in more than 20 % of the patients. In all countries with significant frequency of CNS isolation, they were present as monoculture in about 40 % of cases.

Streptococcus spp. strains were not isolated in Ukraine. Thus, in this country ABSSSI of streptococcal etiology are almost totally absent in the hospitalised patients participating in the analysed IMCCTs. In other countries, the frequency of *Streptococcus* spp. isolation was 7-12 %. It is worth noting that in most cases Streptococci were isolated as part of the associations with other types of microorganisms (Table 3).

The frequency of Enterococci isolation in patients with ABSSSI in the analysed population was 7-24 % in different countries (an average of 8.8 %). It is notable that Enterococci like Streptococcus spp. in the majority of cases were isolated in association with other types of microorganisms (Table 3).

On top of this, 97 patients (9.3 %) had *Acinetobacter* spp. strains isolated and 72 patients (6.9 %) had P. aeruginosa (Table 3). Considering the requirements of the protocols of the analysed IMCCTs on the inclusion of patients who must have Gram-positive etiology of ABSSSI, it is not surprising that in the majority of cases (91 % and 85 % respectively) the strains of *Acinetobacter* spp. and *P. aeruginosa* were isolated as part of the microbial associations. The incidence of these pathogens in ABSSSI significantly varies in different countries. *Acinetobacter* spp. strains were detected in some single cases in Ukraine and Latvia. However, in Poland, Romania, and the Russian Federation the frequency of the isolation of these microorganisms achieved 10 % or more (Table 3). A similar situation was also noted with *P. aeruginosa*. It was almost never detected in patients with ABSSSI in Ukraine and Lithuania, but amounted to 6 % in the Russian Federation and Latvia, and to 12-13 % in Poland and Romania (Table 3).

The incidence of isolated microorganisms that did not fall into the groups described above (a total of 12 types) was statistically insignificant, i.e. was within the acceptable statistical margin of error (≤1 % of the total number of patients with positive results of the microbiological study).

The analysis of the classification of all isolated pathogens (1723 isolates) demonstrated that the frequency of the isolation of Gram-positive and Gram-negative bacteria was 70 % (1208 strains) and 30 % (514 isolates) respectively. A total of 120 different types of microorganisms have been identified (66 types of Gram-positive and 53 types of Gram-negative bacteria). Among all the isolates, 1702 strains are aerobic bacteria and 21 strains are anaerobic. The species composition of the main isolated pathogens is presented in Table 4. It is notable that the majority of the detected types of microorganisms (74 cultures or 62 % of the entire collection) were isolated only in 1-3 patients each, which together amounted to 9 % of the total number of obtained isolates. The presence of these microorganisms in the study patient population can be generally considered a phenomenon. Only 30 types of microorganisms were isolated in more than 1 % of patients each, but all of them together summed up to 91 % of all isolates. Finally, more than two-thirds (68 %) of the total

number of isolates were represented by only six different microorganisms.

The dominant pathogen causing ABSSSI was *S. aureus*, amounting to 40 % of the total number of all isolates. The strains of *S. pyogenes* and other types of *Streptococcus* spp. amounted to 11.7 % and 4.7 % respectively. More than 5 % of the structure of all isolated pathogens were CNS, *Acinetobacter* spp., and *Enterococcus* spp. Other types of microorganisms represented less than 5 % of the total number of isolates (Table 4).

Table 4. Species composition of the microorganisms isolated in patients with ABSSSI participating in the analysed IMCCTs
*Note: * – % of the total number of isolates*

Microorganism	N	%*	Microorganism	N	%*
Staphylococcus aureus	689	40.0	*E.coli*	43	2.5
Streptococcus pyogenes	201	11.7	*Corynebacterium spp.*	28	1.6
CNS	99	5.7	*Morganella morganii*	18	1.0
Acinetobacter spp.	97	5.6	*Stenotraphomonas maltophilia*	19	1.1
Enterococcus spp.	92	5.3	*Citrobacter spp.*	15	0.9
Streptococcus spp.	81	4.7	*Providencia spp.*	8	0.5
Pseudomonas aeruginosa	72	4.2	*Bacteroides fragilis*	7	0.4
Enterobacter spp.	72	4.2	*Alcaligenes faecalis*	5	0.3
Klebsiella spp.	68	3.9	*Pseudomonas spp.*	5	0.3
Proteus spp.	56	3.3	*Serratia spp.*	5	0.3

Considering that the major pathogen causing ABSSSI is *S. aureus* and the most significant problem of the resistance of *S. aureus* is resistance to methicillin, the incidence of MRSA strains in the study patient population was also analysed. The results of the analysis are represented in Table 5. The obtained results show that infections caused by MRSA are detected in 10.4 % of the total patient population. At the same time, in 40.7 % of cases MRSA is isolated in monoculture, i.e. it is the only pathogen causing ABSSSI. Data on different countries show that the frequency of isolating MRSA significantly varies depending on the region.

For example, in Ukraine and Latvia ABSSSI caused by MRSA are present only in single cases and MRSA strains are a small percentage among all microorganisms isolated in ABSSSI (Table 5). In the Russian Federation, MRSA infection

Table 5. Incidence of MRSA strains in patients with ABSSSI participating in the analysed IMCCTs
*Note: * – number of isolated MRSA strains and MRSA isolation incidence in monoculture or in associations*

	Total		RF		Romania		Ukraine		Latvia		Lithuania		Poland	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total number of patients with a positive study result	1,041	–	512	–	181	–	87	–	145	–	74	–	42	–
Incidence of MRSA isolation in patients	109	10.4	50	9.8	40	22.1	1	1.1	2	1.4	10	13.5	5	11.9
In monoculture	44	40.7	18	36.0	17	42.5	0	0.0	1	50.0	5	50.0	3	60.0
In associations	64	59.3	32	64.0	23	57.5	1	100.0	1	50.0	5	50.0	2	40.0
Total number of S. aureus strains	689	–	339	–	130	–	59	–	98	–	50	–	28	–
Share of MRSA among all S. aureus	109	15.7	50	14.7	40	31.3	1	1.7	2	2.0	10	20.0	5	20.0

is diagnosed in 9.8 % of patients, in Poland, 11.9 %, and in Lithuania, 13.5 %. The proportion of MRSA in all isolated *S. aureus* is 14.7 %, 20 %, and 20 % in the Russian Federation, Lithuania, and Poland respectively. MRSA strains were most frequently isolated in Romania, where infections caused by this microorganism were detected in 22.1 % of the patients, while among all the strains of S. aureus, the proportion of MRSA was 31.3 %. The incidence of MRSA in Romania is definitely higher than in all other countries, while in Ukraine and Latvia it is definitely lower compared to the Russian Federation, Lithuania, and Poland.

Discussion

Taking into consideration all the obvious simplicity of the clinical diagnostics of ABSSSI, the microbiological diagnostics and evaluation of effectiveness of the ABMs to treat ABSSSI in clinical studies present many difficulties and much ground for debates.

The main goal of a microbiological study in ABSSSI is the determination of the main pathogen(s) causing the infection process and preventing tissue recovery. However, colonisation of open wounds with different types of microorganisms significantly complicates the possibility of differentiating contaminants and genuine pathogens of the infection process. Isolation of several types of microorganisms in associations also requires the assessment of a likely role of each one of them in the development of the infection process. It is considered that the most virulent among aerobic bacteria, and consequently, the most important etiology agents in ABSSSI are *S. aureus, S. pyogenes, P. aeruginosa*, and Enterobacteria[1].

It is a commonly recognised fact that to obtain trustworthy results of a microbiology study in ABSSSI, it is necessary to obtain biopsy specimens of vitalised tissues from the depth of the wound, or an aspirate / pus from a "sealed" infection site.

In the IMCCTs that we are analysing, the negative results of the microbiological study (the absence of the microorganisms' growth) were obtained in only 74 (6.6 %) patients, which may be considered quite an acceptable number. In addition, this number demonstrates that the protocol of the collection of clinical material for the microbiology study was chosen correctly.

The greatest number of negative results of the microbiology study was demonstrated in Romania (25 out of 209 patients, i.e. 12.0 %) and in Poland (six out of 48, i.e. 12.5 %). Here it should be noted that in both countries the study involved microbiology labs that were part of a unique laboratory holding and, possibly, the obtained data are related to some characteristics of conducting microbiology assays that are general for all of them.

One of the key points when conducting IMCCTs using regional and central microbiology labs is the organisation of the delivery of clinical material from investigative sites to a remote regional or central laboratory. It is known that even when using transport media, long intervals elapsing between the moment that the material was collected and the start of a microbiological study lead to the change in the spectrum of isolated pathogens due to the death of the most fastidious microorganisms (some Streptococci and anaerobes). In our study, only eight patients (0.8 %) had samples of clinical material unsuitable for a microbiology study in accordance with the study procedures (delivered to the regional microbiology lab more than 48 hours after the moment the material was collected). This confirms the acceptability of the choice of the transportation conditions for maximum preservation of the microorganisms' viability. The portion of samples unsuitable for analysis because of delivery to the laboratory later than 48 hours after collection was the greatest in Lithuania (5.8 %), which was related to the logistic characteristics of the

organisation of the study in this country. This fact must be noted when choosing investigative sites and a regional laboratory in Lithuania. In any case, the number of samples whose analysis was impossible due to late delivery to the laboratory or loss during transportation was in our case much less than 15 %, which is the maximum acceptable value for clinical studies.

On the whole, the incidence of the detection of microorganisms in ABSSSI in the analysed IMCCTs was 92.6 % (86-98.6 % in different countries), which is a very good result for such studies.

At the same time, all the analysed IMCCTs were targeted at the selection of patients with ABSSSI caused by Gram-positive bacteria. However, only Gram-negative pathogens were isolated in 8.2 % of the enrolled patients, and only anaerobes were isolated in 0.9 % of the patients. Therefore, the results of the microbiology study of clinical material collected at a screening visit in 9.1 % of the patients did not match the criteria of selecting the patient population. On the one hand, this is the proof of the high level of interpretation of the original microbiological and clinical parameters in the medical centres, while on the other hand, this fact should be taken into consideration when calculating the sample size for such clinical studies.

The highest incidence of isolating only Gram-negative microorganisms out of the clinical material was recorded in Romania (17.1 %), which in combination with a greater number of negative study results (12 %) no doubt requires additional analysis and identifying possible reasons for obtaining such results. At the same time, we should not exclude the problems with either the screening of patients at the level of investigative sites and compliance with the rules for collecting clinical material, or with the performance of the next stages of a microbiology study. However, the most likely reason for getting such results, in our opinion, is a more active use of antibiotics in the pre-hospital setting in Romania than in other CEE countries, which led to Gram-positive microorganisms being identified in the smear when the patient was enrolled in the study, but not growing in the culture due to the antibiotic's activity.

In the analysed IMCCTs considering the strict compliance with the uniform procedure of collecting clinical material for a microbiology study, CNS was isolated in 9.3 % and *Enterococcus spp*. in 8.8 % of the patients with ABSSSI. Considering low virulence of CNS and Enterococci and their frequent isolation as part of microbial associations and not in monoculture, some experts do not consider them as independent etiology agents of ABSSSI[1].

However, it should be noted that all strains of CNS and *Enterococcus spp*. entered in the analysed database were viewed by the investigators as ABSSSI pathogens. The indicators of the frequency of the isolation of Enterococci and, particularly, CNS, significantly varied in different countries (from 7 % to 24 % and from 0 to 20 % respectively). It is notable that in our study in the countries with significant incidence of isolating CNS, these microorganisms in almost half the cases were present as monoculture, i.e. according to the investigators' opinion, CNS were the pathogens that were causing ABSSSI.

According to the data of different international clinical

and epidemiology studies, including the studies conducted in the recent years, Enterococci and CNS are part of the spectrum of the potential pathogens causing ABSSSI, especially in patients with nosocomial wound infections and the presence of coexisting conditions and risk factors (diabetes, implants, immunosuppression, and prior administration of ABMs) [7, 8, 9,10, 11, 12, 13, 16, 17, 21, 22, 23, 24, 25, 26.]

The leading pathogens causing ABSSSI are no doubt *S. aureus* and *S. pyogenes*[7,8,9,10,11,12,13,16,23,25]. According to the data of IMCCTs of new ABMs in patients with ABSSSI presumably caused by Gram-positive bacteria, the share of *S. aureus* and . in such a patient population may reach

90 %[27]. In the studies we analysed we were able to identify an about equally high ratio: *S. aureus*, S. pyogenes and *Streptococcus* spp. were isolated in 66.2 %, 19.3 %, and 7.8 % of the patients respectively, while in some of the patients the associations of *S. aureus* + *S. pyogenes* or *S. aureus* + *Streptococcus* spp. were detected, which equalled respectively to 5.5 % and 2.5 % of the total number of patients with the positive results of the microbiology study.

While *S. aureus* was the major pathogen causing ABSSSI in all the countries, and in almost half the cases it was the only etiological agent of these infections, the incidence of isolating GABHS and *Streptococcus* spp. significantly varied in different countries, and in the majority of cases these microorganisms were isolated as part of associations. As already mentioned above, in some cases the low incidence of isolating S. pyogenes in ABSSSI may be related to the complexity of isolating this microorganism from the infection site even when obtaining a tissue biopsy specimen [14,15].

The results of the analysis of the database also point to the role of Gram-negative bacteria (*Enterobacteriaceae*, *Acinetobacter* spp. and *P. aeruginosa*) in the etiology of ABSSSI in hospitalised patients in CEE. Infections that are caused by the association of Gram-positive and Gram-negative pathogens were detected in 30.7 % of the patients. The incidence of detecting such associations was lower in Ukraine, Latvia, and Lithuania, while it amounted to 30-40 % of cases in the Russian Federation, Romania, and Poland. These data should be taken into consideration in statistical planning of ABSSSI studies in the CEE countries to be able to enroll a sufficient number of patients with Gram-positive pathogens. Apart from this, when planning IMCCTs to treat ABSSSI, the high incidence of mixed infections should be also taken into account and the possibility to prescribe ABMs to fight Gram-negative pathogens, including the strains of *Acinetobacter* spp. and *S. pyogenes*, considering the available local epidemiology data on the sensitivity of different Gram-negative bacteria to antibiotics, should be anticipated.

The main problem of resistance among Gram-positive pathogens of ABSSSI in CEE is the spread of the MRSA strains. Vancomycin-resistant Enterococci (VRE) are widespread in the USA, while they are not a problem for Europe yet[28].

Based on the results of the analysis of the joint database of five IMCCTs that were conducted in CEE, it became obvious that the share of MRSA among all the strains of *S. aureus* generally amounted to 15.7 %. ABSSSI related to MRSA were detected in 10.4 % of the patients. Significant differences in the incidence of MRSA were observed in different countries. It may be presumed that in the centres located in Ukraine and Latvia, MRSA did not constitute a problem, while in the Russian Federation, Poland, and, particularly, Romania, MRSA amounted to 14.7-31.3 % of all strains of this type. The results of MRSA prevalence obtained in our study are generally lower than the published numbers of methicillin resistance among the strains of *S. aureus* isolated in ABSSSI [5a,12,15,29,30]. In the IMCCTs we are analysing here there was no objective to select patients with ABSSSI caused by MRSA. However when planning clinical trials of new ABMs for the treatment of ABSSSI that were presumably or obviously caused by MRSA, the differences in the prevalence of these strains in different CEE countries should be taken into account and the additional procedures of selecting patients to ensure fast enrolment into the study should be anticipated.

Based on the results of the analysis of the microbiological data obtained during the course of IMCCTs in six CEE countries, we can make a conclusion that the strategy used to isolate and identify pathogenic cultures, on the whole proved right. A relatively high technological and scientific level of regional laboratories made it possible to perform a fast and quite trustworthy analysis of available clinical

material. On the other hand, the chosen logistics scheme that included correct selection of the courier company and transportation regime for the clinical material, also helped to minimise the losses. We think that samples which are negative or unsuitable for further analysis constituting only 7.4% is sufficiently low. On the other hand, the isolation of Gram-positive microorganisms in monoculture or in associations in 90.9% of the patients that had demonstrated positive results of the microbiology study, which corresponded to the requirements of the analysed IMCCTs, is proof of quite high medical and technical qualifications of the participating investigative sites. The remarkable quality of the resulting collection of microorganisms pointed to the fact that conducting such IMCCTs in the CEE countries made it possible to investigate new ABMs in the epidemiological context specific to this region.

Conclusion

The results show that the CEE countries should be considered a right place for the evaluation of new antibacterial agents in ABSSSI due to the possibility of isolating a broad spectrum of pathogens and a rather high level of MRSA. It is very likely that Romania is a better country in CEE for conducting such trials because of a 30% MRSA rate in patients with ABSSSI, while most of the patients have community-acquired pathogens.

The presented results of the analysis of the spectrum of bacterial pathogens isolated in patients that participated in IMCCTs of new ABMs to treat ABSSSI presumably caused by Gram-positive or mixed flora give a proper impression of the microbial landscape specific for the participants of such clinical trials in the countries of Central and Eastern Europe. Following a proper procedure for the collection of clinical material for microbiology studies in ABSSSI, use of relevant transport media, and proper organisation of the clinical material delivery from the investigative sites to the regional laboratories help minimise the share of patients who are not eligible for the evaluation of the microbiological effectiveness of the investigated ABMs.

A high level of medical and technical qualification of the investigative sites and regional laboratories makes it possible to effectively conduct the clinical trials of new ABMs in ABSSSI in the CEE countries, and obtain trustworthy results on the microbiological effectiveness of the investigated drugs.

The etiology and antibiotic resistance pattern of the ABSSSI pathogens in patients in the CEE countries detected when analysing the microbiological results of IMCCTs provide an opportunity to properly calculate the sample size and make a solidly-based decision on the participation of investigative sites from these countries while planning similar studies.

Even though this paper was limited to only the analysis of the microbiological data obtained in uniform IMCCTs in patients with ABSSSI in the CEE countries, its results are of obvious practical interest to the companies involved in the development of new ABMs and in the conduct of clinical trials in this therapeutic area.

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As clinical trial activity in the Asia Pacific region continues to expand and contract research organizations (CRO) increasingly provide sponsors with a range of strategic services and support, ACRONET joined the Medidata Partner Program to enhance its technology offerings across the clinical development process. Having already attained its first Medidata accreditation—for Medidata Rave®, the industry's leading electronic data capture (EDC) and clinical data management (CDM) solution— ACRONET plans to implement Rave in at least 15 trials over the next two years.

"Medidata's focus on developing solutions that solve critical challenges for sponsors at every point in the clinical research process is well-aligned with our corporate strategy as well as the goals of our customers," said Hiroyuki Daimon, general manager of ACRONET's clinical IT system department. "In addition to expanding our clinical development capabilities and strengthening our IT solutions, we also expect to benefit from Medidata's strong global presence and broad market demand."

Since 1969, ACRONET has provided a range of global clinical development IT services, including monitoring, data management, statistical analysis and clinical study report creation. As the company evolved its EDC strategy, ACRONET identified Medidata Rave as a critical solution that would improve study efficiency, reduce time throughout the trial process and leverage CDISC standards to easily integrate with other systems. In addition to strengthening relationships with sponsors and sites, ACRONET expects its partnership with Medidata and its Rave accreditation to play a key role the company's ability to increase ROI, expand global reach and uncover new business opportunities.

"ACRONET has a long history of providing high-quality solutions and services to sponsors and distinguishing themselves as a leader in driving clinical development technology initiatives," said Graham Bunn, vice president of partnerships, Medidata Solutions. "With this partnership, we look forward to working with ACRONET to strengthen Medidata Rave's footprint in the Asia-Pac region and build on the growing momentum around our full suite of products."

ACRONET is also considering the other seven accreditations offered by the Medidata Partner Program, which will enable it to further expand the Medidata-related services that it provides to customers. Medidata first announced its channel partner program in April 2005 to enable select CROs and other service providers to offer services in support of Medidata products. Since then, the program has grown to include about 30 partners, ranging from smaller clinical consultancies to large, global CROs.

Source: Medidata Solutions

Sir Chris Evans inspires creation of a £100M Welsh biotech fund

The high-profile biotech investor Sir Chris Evans has inspired the Welsh government to commit £50 million to a new life sciences fund, which will look for matching cash to double the size of the effort. And Evans believes he can rope in private investors willing to contribute £200 million to the cause, potentially setting up an operation with more than $375 million.

Wales is starting out with £25 million now with plans to chip in another £25 million next year. Their goal is to create a biotech hub that can attract venture cash from outside the region and spin out new companies, creating an engine for economic growth. And Evans sees a day when the fund can earn back more money that can continue to be invested in the field.

"We will be looking at doing packages of investment between £500,000 and £10 million in any one company," Sir Chris told a biotech crowd in Wales, according to a report in WalesOnline. "Where it's the bigger number, say £5 million, we would expect some of that to be co-investment which we would bring in from elsewhere in the UK and elsewhere."

Sir Chris is no stranger to big plans. He runs the Merlin venture funds at the Excalibur group and he's been spotlighted as a key figure behind the shadowy NCPharma, which has reportedly gathered substantial backing to launch a major new drug development effort. A year ago he was brought in by the Welsh government to advise officials on biotech policy. He evidently arrived with some ambitious plans.

The news put Wales' biotech industry squarely in the spotlight, a rare occasion for the group. Most of the attention for the country's R&D industry has been centered around Cambridge and in London, where government officials have been working on their own biotech support programs.

Source: JCS Staff Reporter – Jaypreet Dhillon

Adaptive Tools from Aptiv

ER Squared, a clinical trial technology consultancy founded by ex-Bayer executive Robert Musterer, has added another employee. John Fontenault will serve the Connecticut firm as VP of operations. ER Squared advises clients about eclinical challenges, software vendors, biostatistics staffing and data management, among other topics. Says Musterer: "I'm very optimistic. Companies are starting to feel a little less pressure from the economy. People are going to start hiring again and expand their projects again."

The U.S. government launched a modest campaign to promote research participation by the public. It's a generic, uncontroversial website, under NIH auspices, perhaps intended to address public skepticism of science in general and the pharmaceutical industry in particular. The site's

portrait of clinical research is sanitized, with text borrowed from other federal web efforts. There is no whisper of money as one reason for physicians to participate in industry research.

Source: JCS Staff Reporter – Jaypreet Dhillon

Diet Affects Likelihood of Developing Parkinson's Disease

New research suggests that the way people eat may impact whether they develop Parkinson's disease (PD). Two studies, one carried out at a PDF Research Center at Columbia University in New York and published in the journal Movement Disorders and another carried out at hospitals in Japan and published in the European Journal of Neurology, found that adherence to a particular type of diet was associated with reduced odds of having Parkinson's.

Previous research suggested that diet might play a role in the development of Parkinson's. In particular, a single large study found that people who consumed a diet high in vegetables, whole grains, fruits, and legumes along with moderately high levels of fish but low to moderate levels of dairy, meat, and poultry — the so-called "Mediterranean-style diet" — had a lower chance of developing Parkinson's.

In these two studies, researchers from a large Japanese consortium of neurologists called the Fukuoka Kinki Parkinson's Disease Study Group in Japan and a PDF-supported group at Columbia University led by Roy Alcalay, M.D., M.Sc., both followed up on those previous findings. They recruited groups of people with and without Parkinson's, and used surveys to collect data on what people in each group ate. They then looked to see whether there was a significant association between the types of diets people consumed and whether they had Parkinson's.

Source: CenterWatch

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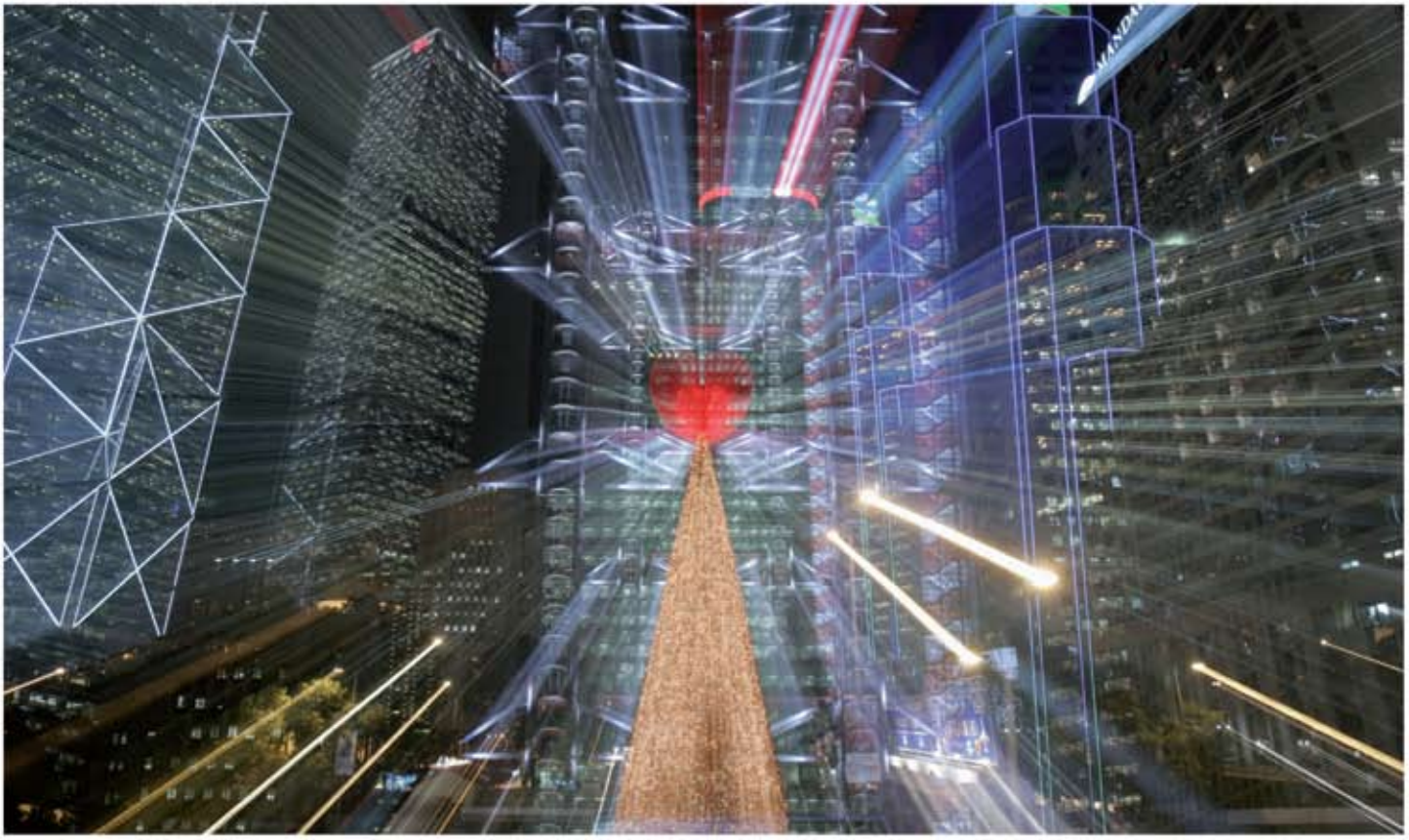

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