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Oncology Trials

APPLIED CLINICAL TRIALS

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A survey on the perception of European pediatricians and industry/CROs.

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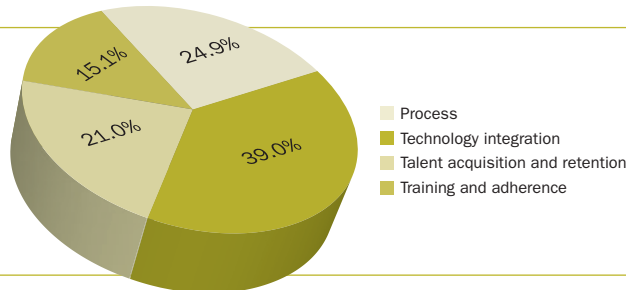
Blogs

The most popular blogs from 2013 have been bundled in one linkable blog on the website. The most popular? Tips on Writing Risk-Based Monitoring Plans. Visit <http://bit.ly/1amRyRJ> to read the rest.

eNewsletters

Upcoming topics for eNewsletters the next two months include: Risk-Based Monitoring 2/6; IRBs 2/20; Clinical Supply Chain 2/27; Training/Education, 3/6; Patient Engagement, 3/13; and Trial Design 3/20. Register at <http://bit.ly/NBvcNx> to receive directly to your inbox.

What is our biggest challenge with technology?



Source: *Applied Clinical Trials* Clinical Technologies Survey, October 2013. Visit www.appliedclinicaltrials.com/ClinTech

eLearning

Cloud Computing and Other ClinTech Challenges

This webinar looks at results from a recent *Applied Clinical Trials* and ClinTech, a CBI event, survey exploring clinical technologies. Analysts and experts will discuss the clinical technology landscape for 2014 and beyond. www.appliedclinicaltrials.com/clintechwebcast

Risk-Based Monitoring: Models, Myths and Momentum

This webcast will look at the current state of clinical monitoring through recent surveys; discuss the various models under the umbrella term of "risk-based monitoring" and highlight many of the challenges and barriers to changing monitoring models. www.appliedclinicaltrials.com/monitoring

Using ePRO in Large Comparison Trials

Gilead Sciences wanted to assess the efficacy of Ranolazine compared to placebo on reducing average weekly angina frequency in subjects with type 2 diabetes mellitus, coronary artery disease, and chronic stable angina who remain symptomatic despite treatment with one or two antianginal agents.

In previous trials, Ranolazine had been proven as an effective antianginal treatment in patients with clinically manifest CAD, both as monotherapy and in combination with other commonly prescribed medications as add-on therapy.

Previous Ranolazine studies used exercise treadmill parameters as the primary endpoint. While effective and easily verifiable, attaining

the data was costly, provided numerous logistical challenges, and bore questionable clinical relevance, especially at the level of the individual patient. Other possible endpoints such as number of angina episodes and sublingual nitroglycerin use imparted concerns about using patient diaries to collect endpoint data.

Paper diaries have proven to be inaccurate, although it is difficult to measure actual protocol compliance without time stamps. One study showed paper compliance to be as little as 11% when reported compliance was 90%.²

Carolyn Peterson, Marketing Manager at PHT Corporation

Visit <http://bit.ly/1aN2moP> for the full version of this article

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Streamline Trial Operations with Cloud Opportunities

eTMF applications provide a strategic asset in the drive for greater efficiency in clinical trials.

Jennifer Goldsmith, Vice President, Veeva Vault for Veeva Systems, spoke to *Applied Clinical Trials* about the changes in life sciences technology that are improving increased collaboration. Specifically, companies are taking information out of silos to share documents and data in cloud-based systems. For clinical trials in particular, Goldsmith says rapid adoption of cloud-based solutions provides benefits such as speeding study start-up, improving monitoring, improving inspection readiness and easing collaboration with external global partners.

A recent survey of clinical trials professionals showed mixed opinions on cloud technology and a significant percent admitted being confused by cloud. Can you comment on the results?

The survey shows that people continue to find the cloud and the term cloud confusing. When Veeva says cloud, we are really talking about multi-tenant Software as a Service (SaaS). But there is confusion because some use the term cloud when in actuality they are simply systems hosted in a different location.

Multi-tenant SaaS has many benefits over hosted systems, including software that is always up-to-date, with the most current capabilities. It also is possible to avoid massive upgrade processes that are seen with on-premise systems.

The leading response from 34% of



Jennifer Goldsmith, Vice President,
Veeva Vault for Veeva Systems

the respondents was that they viewed cloud as cost-effective. This is important because cloud is the ultimate democratization. Cloud allows small- and medium-sized businesses to adopt enterprise quality technology that they could not afford in the past. So it brings the best capabilities to companies of all sizes within the life sciences industry.

How can cloud improve trial operations?

One of the greatest challenges facing the clinical trials area is the ability for sponsors, investigators, and CROs to work together in a collaborative environment—without needing to exchange information via overnight documents to multiple locations, or waiting for infor-

mation to come at the end of the study. Cloud can really improve collaborative business processes.

Collaboration breaks down when there are separate systems for exchanging and managing TMF documents. Some companies have a portal that allows them to exchange information with investigators and CROs and then they have a separate and distinct content management system to manage that information as it comes into the electronic Trial Master File (eTMF). We created an investigator portal that extends the eTMF itself, so when investigators at the site upload a 1572 or CV in the portal that information is being routed directly into the eTMF without an interim step.

How can organizations begin to turn their eTMF into a strategic asset?

There are important steps to take to leverage the eTMF as a strategic asset. First and foremost is to get the information and the processes electronic. Some organizations are still working with paper-based processes and scan-to-digital for filing. Electronic information opens a new world of capabilities—whether searching for information or automating manual steps, electronic is critical. If your information is not electronic throughout the collection, QC and monitoring processes, then your eTMF isn't generating the data it needs to deliver strategic insights.

Step two involves collaborative pro-

cesses. Since work spans sponsors, CROs, and investigators, the electronic processes or workflows should span all three parties as well. Traditionally, documents are managed in one or more repositories, exchanged via email or FedEx, and tracked in spreadsheets. It is impossible to have efficient operations when collaboration is splintered across separate systems. When the eTMF provides all three functions—document management, exchange, and tracking—across all three parties, you see a huge leap in productivity.

The third step in the process is creating a repeatable framework. Companies should establish a common understanding of what's needed, what's it called, who provides it, and when. This blueprint gets built into the eTMF and keeps everyone working to a common goal.

Also, a repeatable framework supports repeatable processes. This means that companies can operationalize their SOPs, not just follow written SOPs. Many of us have had to read and understand SOPs throughout the course of our career, and many of us can say that those SOPs, once read and understood, went into a drawer that nobody looks at until the next time you have to verify that you have read and understood those SOPs. By operationalizing that process in the form of a workflow or automated business process, it helps people work seamlessly with one another, and ensures that they are following a common process.

The final piece in leveraging the eTMF as a strategic asset is around metrics. Measuring performance is absolutely critical when driving process improvements. This requires defining the right metrics and ensuring they are reflected in the eTMF system

workflows and reports. This allows companies to garner new information specific to how a process runs, and how efficiently it runs. The information can also be strategic, for example, to identify which sites are better for which therapeutic areas, which sites have faster study start-up and why, and which service providers can the sponsor work with most effectively.

How can organizations make the most of their eTMFs?

An eTMF represents an opportunity for clinical organizations to gain three things: better access, better visibility, and better control of their information. These high-level concepts have a wide-ranging impact on the clinical trials process overall, such as speeding site and study start-up. Visibility, access, and control also impacts and improves inspection readiness. Inspection readiness has been a hot topic because in paper-based environments, it's incredibly difficult to determine what is or isn't inspection ready. It takes a lot of time and manual effort to track what's complete, what's missing, and to correct mistakes. TMF applications on the other hand provide real-time visibility into overall inspection readiness. Also, in terms of auditing, eTMFs can support remote auditing of information. We are seeing this as a growing trend for regulatory agencies globally. The MHRA, for example, has stated a preference for remotely auditing the trial master file.

Can you describe Veeva Vault?

Veeva Vault is the first cloud-based content management system for regulated content. Built from the ground up for the life sciences industry, it supports 21CFR Part 11 compliance, Annex 11 compliance, and GxP-related

requirements. We also built a suite of applications serving the most content-intensive areas of the business—everything from eTMFs in the clinical space, to regulatory submissions in the R&D space, to SOPs and batch records in the quality and manufacturing space; and even to medical affairs and promotional materials on the commercial side of the house. This is the first time that a software company has built both the platform and applications for life sciences content, and there is unprecedented control when you can manage documents from end-to-end across the enterprise.

VEEVA SYSTEMS

Veeva Vault eTMF improves trial efficiency by giving both sponsors and CROs secure access to documents and status reports throughout the study duration. With Vault eTMF, you create, exchange, and update all documents in one location: the cloud.

Vault Investigator Portal speeds collection of all trial-related content through a single interface that is a part of Vault eTMF. Veeva's multi-study model brings sponsors, sites, and CROs together for more efficient collaboration and population of the eTMF.

Veeva is a leader in cloud-based software for the global life sciences industry. Committed to innovation, product excellence and customer success, Veeva has over 170 customers, ranging from the world's largest pharmaceutical companies to emerging biotech. Founded in 2007, Veeva is headquartered in the San Francisco Bay Area, with offices in Philadelphia, Barcelona, Budapest, London, Paris, Beijing, Shanghai, Osaka, Tokyo, Sydney, and Singapore.

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GLOBAL NEWS

How to Improve the Quality of Research Reporting

Making advances in the appropriateness of research design, methods, and analysis are essential to increase value and reduce waste in clinical studies, particularly because these “correctable weaknesses” can produce misleading results, according to leading experts.

“To maximize motivation for change, reductions of waste in research will need behavioral changes, not only from researchers, but also from publishers and regulators. These changes will need external pressure from stakeholders such as funding agencies,” noted John Ioannidis, PhD, Professor in Disease Prevention in the School of Medicine and Professor of Health Research and Policy in Stanford, US, and colleagues in an article published by *Lancet* on January 8. “Funders are eager

to ensure that they get a good return on their investments; inadequate research diminishes the fiscal investment that they have made. Patients and the public also have an important voice.”

They concede that minor effects can be difficult to distinguish from bias introduced by study design and analyses. However, an absence of detailed written protocols and poor documentation of research appears to be surprisingly common and insufficient consideration may be given to both previous and continuing studies, and arbitrary choice of analyses and an overemphasis on random extremes might affect the reported findings.

Several problems relate to research staff, including failure to involve experienced statisticians and methodologists,

the lack of training for clinical researchers and laboratory scientists in research methods and design, and the involvement of stakeholders with conflicts of interest. Inadequate emphasis is placed on recording of research decisions and on reproducibility of research, while reward systems incentivize quantity more than quality, as well as novelty more than reliability, the authors continued.

To address these problems, they propose improvements in protocols and documentation, consideration of evidence from studies in progress, standardization of research efforts, optimization and training of experienced and non-conflicted scientific workforce, and reconsideration of scientific reward systems, among others.

—Philip Ward

VIEW FROM WASHINGTON

FDA, Sponsors Continue Quest for More Efficient Clinical Trials

The decline in important new medicines reaching market in 2013 has produced multiple proposals for making clinical trials more effective and efficient. A December report from Deloitte and Thomson Reuters analyzing R&D spending by 12 leading biopharma companies describes lower return-on-investment from clinical research, which has contributed to a steady rise in the cost of taking a new drug from discovery to launch (up 18% from 2010 to reach \$1.3 billion in 2013). For improvement, analysts advise sponsors to curb late-stage research “leakage,” reduce research cycle times, use more appropriate outsourcing, seek out and enhance R&D talent, and bolster analytic capabilities.

A January 2014 outlook report from the Tufts Center for the Study of Drug Development emphasizes the need for more realistic assessment of the chances for success of candidates as key to curbing

late-stage clinical development failures. CSDD Director Ken Kaitin advised sponsors to reassess their use of meta-analyses and sub-group analysis to justify pushing compounds forward in development despite poor Phase II results. He expects to see continued FDA encouragement for breakthrough drugs, adaptive clinical trial designs in earlier studies, and greater use of patient-reported outcomes (PRO) and social media to communicate with patients.

FDA seeks to encourage sponsors, academics, and expert coalitions to research and seek qualification of such approaches, as seen in new guidance issued last month describing the “Qualification Process for Drug Development Tools” (DDT). This document, prepared by CDER’s Qualification Process Working Group, describes FDA’s qualification process, including agency procedures

for interacting with parties developing DDTs and its review of data submitted to support acceptance of new DDTs. FDA also explains how it will increase communication on its qualification decisions in order to make DDTs widely available to the research community for use in developing other medical products.

The complexities in utilizing PRO instruments is reflected in a draft guidance published as an attachment to the DDT guidance on the use of EXACT (Exacerbations of Chronic Pulmonary Disease Tool) in measuring symptoms of exacerbation of chronic bronchitis. Although this is a qualified endpoint for Phase II studies, FDA notes uncertainty in defining the target population and in using this measure in confirmatory clinical trials. PROs have long raised controversial issues, and continue to do so.

—Jill Wechsler

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VIEW FROM BRUSSELS

New Horizons in Research Funding for EU

Horizon 2020—the European Union’s newly-agreed seven-year multi-billion research program is one of the few areas of the EU’s new budget that sees a major increase in resource—roughly 30% up on its predecessor program. And according to the triumphant announcement of the commissioner, “Horizon 2020 will fund not just the best fundamental research, but also applied research and innovation, bringing in small and large companies.”

For those interested in clinical trials, the most interesting elements of this vast program are doubtless within the public/private partnership on innovative medicines, and on aging populations, poverty-related diseases, and support for smaller firms. The EU insists that it is keen on helping smaller firms’ research and innovation. The commissioner cites new financing options in the form of risk-sharing through guarantees or risk finance through loans and equity to support innovative companies.

At the heart of the drug development element of the program is IMI2—the follow-up to the Innovative Medicines Initiative that has seen industry and the EU working together for the last seven years in a \$2.5 billion joint sponsorship of early-stage research. Horizon 2020 envisages an expansion of this public-private exercise under IMI2, and the approach has won support from industry and from national governments. The EU has moved ahead of the necessary full endorsement of the plans by giving notice that it will offer research grants of more than \$1 billion for drug-related research early in 2014, ranging across therapeutic categories, technologies, and disciplines.

Under the umbrella title of personalizing health and care, nearly \$500 million is promised for projects in advanced therapies, new diagnostic tools and technologies, predictive human safety testing, pediatric treatments, and

improving understanding of disease through systems medicine and investigation of common mechanisms of diseases and co-morbidities. There is further support available for personalized medicine development under another package, part of which will be devoted to translating ‘omics’ into stratified approaches to advance health promotion and disease prevention, and part to screening and prevention programs, new in vitro diagnostic tools and assays, and new models for efficient prevention-oriented health systems. A further \$200 million is slated to fund clinical research on regenerative medicine, and vaccine development for HIV/AIDS. The funds will also go to wider use of information technology in early risk detection and intervention; integrated care and patient self-management; eHealth services; and improved diagnosis and treatment.

Parliament precaution

The lead committee in the parliament will introduce both general and specific limitations to IMI2. IMI2 “should not fund all clinical trials, but only those which have an innovative turn to them.” And it wants to intervene in the definition of acceptable research. “Those partnerships should reflect a balanced contribution from all partners, be accountable for the achievement of their targets, and be aligned with the EU’s strategic goals relating to research, development and innovation. The governance and functioning of those partnerships should be open, transparent, effective, and efficient, and give the opportunity to a wide range of stakeholders active in the specific areas of those partnerships to participate.”

The parliament also wants to trammel the process with additional criteria—“in particular, principles on gender equality and open access,” among others. Some members of the parliament are urging that the program’s priorities shift from

therapy and towards prevention, and that no support should be given to clinical trials beyond Phase II.

Simmering opposition

In advance of the committee vote in late January, the European Alliance for Personalized Medicine (EAPM) came out with a detailed statement strongly supporting “the IMI2 contribution to achieving the goal of personalized/stratified medicine across the EU.” IMI2 is “a key EU initiative that can...bring about a balanced and added-value reworking of the R&D cycle. But limiting the activities in the IMI2 proposal, in particular clinical research, will seriously stall the development of lifesaving treatments.”

In particular, EAPM says amendments calling for a ban on Phase III and IV trials “are too extreme and would jeopardize the ability of IMI2 to deliver innovative research, development prevention and treatment solutions for critically ill patients.” It points out that in the area of rare diseases, for example, late-stage R&D carries a high risk of failure, and the EU should therefore provide real incentives to all parts of the research community, in particular academics and smaller firms, to participate. EAPM believes it is crucial to attract outside investment to Europe-led projects.

Before the debate moves on to its final stages in February, other similar warnings and admonitions are likely to emerge from other researchers. Many of the proposed amendments are well-intentioned and match Europe’s cautious zeitgeist in relation to research. But too much well-meaning interventionism has repeatedly handicapped Europe’s bid to create an environment conducive to research, and the brave new world that EU rhetoric is promising is at risk of being reduced to a timid old formula of excessive intrusion.

—Peter O’Donnell



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FEATURED FOCUS: CRO/SPONSOR PARTNERSHIP

Fine-Tuning CRO/Sponsor Interaction

The problem with overbearing project managers on the sponsor side of the pharma/contract research organization (CRO) equation is that they dynamite the efficiencies CROs are hired to deliver.

“Micromanagement hurts us in the long run,” said Colleen Cox, Senior Manager, Data Management at Infinity Pharmaceuticals, at CBI’s Sponsor/CRO Systems & Business Process Integration conference in Raleigh, NC this past November. Pharma doesn’t always like ceding control to external groups, but it’s necessary, said Cox. Apart from slowing down a project, micromanagement also “damages trust” between partners, she said.

Ian Lauf, Associate Director, Clinical Alliance Management at Eisai, countered that consistent oversight isn’t the same

as micromanagement, noting regulatory authorities “need to know the sponsor is in charge.” However, Lauf agreed sponsors sacrifice key CRO efficiencies—like speed—when they “force their SOPs on their partners,” rendering CROs into extensions of internal employee personnel.

Stefan Proniuk, VP of Product Development at Arno Therapeutics, a virtual company focused on early stage development, said Arno doesn’t have the resources to micromanage its CRO partners, even if it wanted to; small virtual biotechs live and die by the performance of their partners, and the CRO’s ability to hit deadlines for investors. “Venture capitalists want their money back in five years,” said Proniuk, adding that for early-stage virtual companies, the process beginning with preclinical

chemistry, manufacturing and control, and toxicology studies, and ending with the conclusion of Phase II trials should last 48 months, maximum. For virtual companies, the four most important CRO capabilities, per Proniuk, are: speed, speed, speed, and quality, which can’t be compromised.

As pharma and CROs shift toward integrated partnering models that put CROs on more equal footing with drug sponsors, pharma will need to reexamine and focus on its remaining key competencies, and make tough decisions about internal headcount as more functions are outsourced.

—Ben Comer, Senior Editor, *Pharmaceutical Executive*

Editor’s Note: CBI, *Applied Clinical Trials*, and *Pharmaceutical Executive* are owned by Advantare Communications.

DATA ANALYSIS

BRIC Expenditures Increasing at a Much Faster Pace than US

Clinical subject expenditures are sizable and represent an average of 5% of per-patient budget of later phase clinical trials. Relative subject reimbursement costs can play a large role in which region to select.

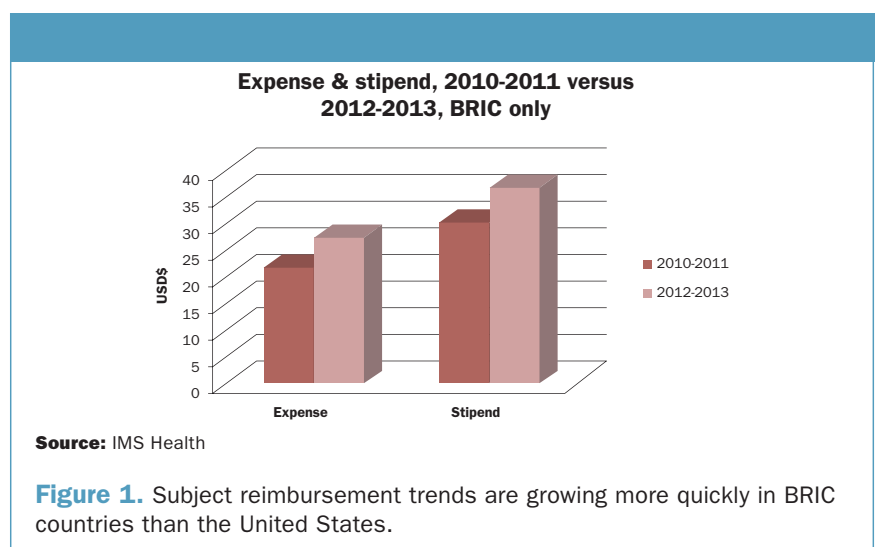
IMS Health maintains current data on relative costs of clinical subject reimbursements around the world in the GrantPlan database, which contains the clinical investigator grants for sponsor companies and CROs that conduct over three quarters of all commercial clinical trials.

Current analysis demonstrates the reimbursement per subject in these emerging geographies is growing more rapidly than in the more established US region. The United States has been averaging 8% annual expense increases and ~1% stipend increase from 2011-2013, while reimbursement costs in BRIC countries (Brazil, Russia, India, and China) are growing

at two times those rates, with ~20% expense increase and 17% stipend increase. Russia is by far the highest increase. Even if BRIC countries are starting off on a

lower base compared to the US, the rapid rise in cost in these regions warrant our careful consideration in the coming years.

—IMS Health



Q	P	A	O	B	A	T	J	A	K	A	V	I	W	L	J	ARZERRA
O	Q	M	K	M	R	X	C	G	B	I	S	D	L	Y	J	AVONEX
S	O	V	F	R	A	E	U	L	Z	L	V	O	C	G	I	JAKAVI
J	X	L	C	W	D	Y	V	X	O	V	I	E	T	Y	M	NEXAVAR
H	B	C	W	F	O	P	Z	Y	L	B	F	D	O	A	A	SUTENT
Y	Q	J	V	K	L	Z	Y	L	T	A	U	E	V	L	E	TYVERB
R	R	D	E	Y	E	G	B	R	H	R	V	O	Q	K	Z	VELCADE
E	A	O	L	M	X	D	K	U	W	R	N	P	V	C	E	XALKORI
I	C	V	C	F	T	J	X	G	N	E	X	K	G	I	Z	XELODA
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M	S	G	S	E	V	I	H	X	F	B	B	R	C	R	B	

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A New Look at Global Study Volunteer Experiences with Informed Consent

A discussion of summary findings from the CISC RP 2013 Perceptions and Insights Study

The Center for Information & Study on Clinical Research Participation (CISC RP), an independent non-profit organization, recently conducted a global assessment of study volunteer experiences with the informed consent process. The results of this study show wide variation between study volunteers by age group and by geographic region and suggest opportunities for general as well as targeted improvement.

The online study was conducted among a global community of health information seekers and research participants. Overall, nearly 6,000 people provided complete responses, making CISC RP's 2013 Perceptions & Insights Study one of the largest international surveys ever conducted among clinical research participants.

It has been nearly 10 years since such an assessment has been conducted. During that time, protocol complexity has increased dramatically. In 2012, according to the Tufts Center for the Study of Drug Development, in a typical Phase III protocol each study volunteer had to complete nearly 170 procedures during the course of 11 visits across 230 days. This represents more than a 60% increase in the number of procedures performed in 2002. Patients from an average of 34 countries

and 196 research centers were recruited for that typical Phase II clinical trial, up from 11 countries and 124 research centers 10 years ago. And with increasing focus on stratified patient populations, in 2012 each study volunteer had to meet an average of 50 eligibility criteria in order to participate in that typical Phase III study—up from an average of 31 inclusion and exclusion criteria ten years ago.

Despite efforts to simplify the informed consent form and improve comprehension during the past decade, in this latest study a higher proportion of study volunteers report finding the informed consent form difficult to understand compared with the results of past surveys. In addition, a significantly higher proportion of study volunteers in both South America and Asia Pacific find the informed consent form difficult to understand ('somewhat difficult' and 'very difficult' combined). The vast majority of study volunteers, overall and by region, report that their clinical trial expectations were ultimately met. What follows is a discussion of summary findings from the CISC RP 2013 Perceptions & Insights Study. For a series of detailed reports on this latest study, organized by topic, please visit www.ciscrp.org.



Kenneth A. Getz
MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISC RP, both in Boston, MA, e-mail: kenneth.getz@tufts.edu

About the study

CISC RP conducted the Perceptions & Insights Study online in the spring of 2013, following feedback from a global community of patients and the public indicating their preference for receiving and completing a survey using this distribution channel. The survey instrument included questions posed in past surveys conducted by Harris Interactive, CenterWatch, and CISC RP, as well as new questions. Representatives from pharmaceutical and biotechnology companies, contract research organizations and investigative sites provided input into the questionnaire design. A central ethical review committee reviewed the final survey instrument.

CISC RP collaborated with Acurian for its help in reaching and engaging respondents around the world. Acurian maintains a proprietary database of people who have explicitly opted-in—via online and offline consumer health surveys—to receive healthcare information on specific diseases and clinical trial notifications.

A total of 5,701 international respondents completed the survey with the highest concentration (75% or n=4,286) based in North America; 15% (n= 837) based in Europe, 5% (n=233) from South America and 5% (n=329) from Asia-Pacific. A majority of respondents (58%) are female. Approximately four-out-of-ten respondents had participated in a clinical trial prior to completing the online survey. Respondents diagnosed with an illness represented a very broad mix of disease indications. Approximately 20% (n=1,042) of respondents were under the age of 34; and the majority (n=4,659) were 35 year and older.

Global differences in comprehension

The vast majority of study volunteers responding to this survey reported having an initial informed consent review experience using a printed form. Only 9% reported having a video or electronic informed consent review. The results of this 2013 study should serve as a reasonable baseline for assessing the impact of

Global patient experiences with informed consent				
	NORTH AMERICA	EUROPE	SOUTH AMERICA	ASIA-PACIFIC
Percentage who found the informed consent form difficult to understand (e.g., 'Somewhat Difficult' and 'Very Difficult' combined)	12%	41%	63%	69%
Percentage who reviewed the informed consent form alone	11%	12%	18%	10%
Percentage who were more willing to participate after informed consent form review	50%	59%	51%	68%
Percentage who never received updates about the study after informed consent form review	23%	17%	7%	8%

Source: CISCRP's 2013 Perceptions & Insights Study; N = 5,701

Table 1. Across the board, patients were more willing to participate after a review of the informed consent form.

e-consent forms and other progressive approaches as their adoption increases.

Overall, nearly six-out-of-ten study volunteers initially read the informed consent form by themselves. Outside of North America, due in part to varied levels of literacy and to greater dependency and trust in their relationships with medical professionals, a significantly lower percentage of study volunteers—30% of South American, 46% of European and 23% of Asia-Pacific—report independently reading the informed consent form at the outset of their participation.

Approximately three-out-of-four study volunteers reviewed the informed consent form with study staff, with most reviewing the form with a study coordinator. A significantly higher percentage of study volunteers in South America and Asia-Pacific review the informed consent form with the principal investigator (39% and 48% respectively). One-in-ten study participants reports they do not review the informed consent form with anyone. Interestingly, nearly double that percentage—18%—of study participants in South America reported that no one reviewed the informed consent with them suggesting an opportunity for attention and remediation.

The majority (85%) of study partici-

pants, overall, say they are “Somewhat Satisfied” or “Very Satisfied” that their questions were answered during the informed consent form review process, and 15% say that they were not satisfied. A significantly higher percentage (approximately one-third) of study volunteers outside North America is less satisfied that their questions were answered during the informed consent review process. And a much higher proportion (28%) of study volunteers in the 18-34 year-old age group were also less satisfied that their questions were answered during the informed consent form review.

One-out-of-five study volunteers reports finding the informed consent form to be “Somewhat Difficult” or “Very Difficult” to understand. Compared to past surveys conducted among global communities of study volunteers, this is the highest percentage ever recorded. A very high percentage of study participants in South America (63%) and in Asia-Pacific (69%) found their informed consent forms difficult to understand suggesting that a number of factors including language translation quality and study staff effectiveness in conducting form review are falling short. Four-out-of-ten study participants in Europe also found their informed

consent forms difficult to understand.

The results of this study also suggest that younger study volunteers may require customized approaches to informed consent form development and review. Half of 18-34-year-old study participants worldwide found their informed consent forms “Somewhat Difficult” or “Very Difficult” to understand. Among 55-year-olds and up, 90% reported that the informed consent form was “Not at all Difficult” to understand.

Although a high percentage of study participants outside of North America and in the 18-44 age group consider the informed consent form difficult to understand, a relatively high percentage of all study volunteers—including these subgroups—say that they were “Somewhat More Willing” or “Much More Willing” to participate following their review of the informed consent form. A significantly higher percentage of study volunteers in Europe (59%) and Asia Pacific (68%) said that that they were more willing to participate following their review of the informed consent form. This review process is likely contributing to volunteer rapport with the study staff. The protocol's scientific complexity and its stringent eligibility requirements may also play a part in elevating study volunteer interest in participating.

Conclusion

The results of the 2013 Perceptions & Insights Study provide insights into opportunities to build on and improve patient experiences. A relatively small proportion of study volunteers are not reading or reviewing the informed consent form with wide differences observed in emerging regions suggesting an inconsistently executed process. The results also show that, compared to historical levels, an even higher percentage of volunteers find the informed consent form difficult to understand.

But overall, the informed consent process receives generally strong marks in terms of study volunteer satisfaction that their questions were answered and that their expectations of the clinical trial were met or exceeded.

How to Improve Clinical Research in Children

Martine Dehlinger Kremer, PhD, Piergiorgio Galletti, Michela Masoero, Amparo Alemany Pozuelo

A survey on the perception of European pediatricians and industry/CROs.



Since January 2007, the European “Pediatric Regulation”¹ has fostered ethical research and ensured appropriate authorization and information on medicines for children. The challenging nature of pediatric clinical research requires competence for a full appreciation of the evolving clinical trial methodology in this setting, and a deep knowledge of the specific regulatory requirements. The Pediatric Working Group of the European CRO Federation (EUCROF-PWG) first analyzed the status of pediatric clinical research in Europe by conducting a survey in 2007.² The results revealed a relatively low number of ongoing pediatric trials while it was expected that the European Pediatric Regulation would stimulate more pediatric research. Based on the information in the public European clinical trials database (EudraCT), the number of authorized pediatric trials, which were part of an agreed Pediatric Investigation Plan (PIP) was 70 in 2011, representing 19% of all pediatric studies.³ According to the recent report of the Pediatric Medicines Section that evaluated research activities during 2011, and that was submitted to the European Medicines Agency (EMA), pharmaceutical companies seem to be meeting their clinical trial obligations in view of a marketing authorization. However, some major deviations from the rules set by the Regulation were observed, in particular, often poorly justified late submissions of PIPs/waiver applications and slow progress of the clinical trial plan.⁴ Nonetheless, further research incentives are provided by the EMA through the EU Framework Program by fund-

ing studies for off-patent medicinal products, in view of the submission of a Pediatric Use Marketing Authorization (PUMA). This program will hopefully give further impulse to pediatric research, but will also amplify the need of quality improvement in pediatric clinical research.

Another survey performed by the EUCROF-PWG in 2009 aimed to determine the main difficulties and constraints in pediatric research among European CROs, pharmaceutical companies, and Institutional Review Boards/Ethics Committees (ECs).⁵ Most respondents reported to have conducted less than five clinical trials in children over the last three years. From the responses, it was evident that there was space for improvement in the application of an appropriate methodology, but also a need for support. In particular, support is needed for a better understanding of how to design pediatric clinical trials, how to select appropriate and validated endpoints, how to write good Patient Information Sheets (Informed Consent and Assent Form), and, for ECs, how to gain more experience in the process of pediatric study protocol assessment.

A follow-up survey was launched in 2011 by the EUCROF-PWG to evaluate the current situation relating to pediatric clinical studies and to determine whether the concerned stakeholders had gained more experience in pediatric clinical research. The analysis involved the number of studies conducted, the difficulties encountered in conducting clinical research with children, the perception of the need for external support and the experience/competence of the ECs. This last survey was addressed to

pediatricians, pharmaceutical/biotech industry, and CROs in Europe in order to collect different points of view and provide a framework for the assessment of the status of pediatric clinical research. The present article reports the results of this last survey, and identifies current strengths and weaknesses in pediatric clinical research and the evolutionary pattern of the approach to pediatric drug development since the introduction of the European Pediatric Regulation.

Survey Results

Of the 350 questionnaires sent out (60% of these to CROs/pharma companies; 40% to pediatricians), 58 were completed and returned. The response rate was 13% from companies and 20% from pediatricians. Respondents who declared not to be involved in clinical research in pediatrics did not provide information so that they were not considered for statistical analysis (N=2).

Out of 56 respondents evaluated, 29 (51.8%) were pediatricians (mostly from academic institutions or general hospitals), 15 (26.8%) were CROs (mostly country affiliates), and 12 (21.4%) were pharmaceutical or biotech enterprises (mostly ranking within the top 10 in the local markets). The data analyses have been conducted separately for pediatricians (N=29) and sponsors/CROs together (identified hereafter as "companies:" N=27). Sponsors and CROs data were pooled because they have similar roles in carrying out clinical trials. Results are reported as percentages of responses in each category analyzed.

Knowledge of the Pediatric Regulation 1901/2006/EC. The knowledge of the Pediatric Regulation 1901/2006/EC is widespread among respondents (93% within companies; 83% among pediatricians), thanks to a direct involvement in pediatric studies which represent a main source for familiarization with the regulation. Although about 70% of companies and pediatricians believe that the Pediatric Regulation might eventually lead to favorable effects on the therapeutic needs of the pediatric population, it is surprising that there is moderate expectation of the Pediatric Regulation to impact effectively on the availability of new medicines authorized for children, and even less regarding the availability of new indications, new formulations, or an impact on off-patent drugs (Table 1).

It is noteworthy that the awareness of the likely increase of costs in public health, which can be an effect of the increased research activities and related costs, is evidently low (10% to 11%).

Experience in clinical research with children. 63% of companies reported to have started no more than two pediatric studies in the past three years (including 25% of companies reporting no studies at all). Data reported by pediatricians were biased by a high rate on non-responders to this question (56%); the remaining 44% of pediatricians was evenly distributed among the categories listed in Table 2.

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Impact of Pediatric Regulation		
IMPACT	COMPANIES (N=27)	PEDIATRICIANS (N=29)
With regard to drug development:		
on new medicines not yet authorized	59 %	62 %
on new indications	22 %	45 %
on new formulations or dosage forms	19 %	28 %
on off patent drugs	11 %	10 %
With regard to pediatric health:		
on the development of innovative drugs	41 %	62 %
on therapeutic needs	70 %	69 %
on improving planning / managing clinical research	33 %	21 %
on increasing profitability of existing drugs	26 %	21 %
on increasing work; no impact on therapeutic needs	4 %	3 %
on increasing costs in public health (multiple choices allowed)	11 %	10 %

Source: Kremer, et al.

Table 1. Expected impact of the Pediatric Regulation across drug development and pediatric health.

Because clinical research plays a dominant role in the final availability of new drugs, we have investigated the level of experience in the various phases of the clinical development. Good or fairly good experience (relating to a four-level scale: good—fairly good—poor—none) has been reported especially in Phase II and Phase III studies while Phase I has been identified as the area with less experience. Observational studies were mostly performed by pediatricians, as non-commercial sponsors of such studies. Large experience was reported by both companies and pediatricians mainly in oncology, vaccines and hematology.

Difficulties in performing clinical research with children. Difficulties related to protocol development, ethical aspects and practical issues can be encountered in this population. These were investigated (Figure 1) and both practical and methodological aspects appear to be critical while designing and carrying out a pediatric study. Obtaining the parents' understanding and consent is reported as critical and represents a frequent difficulty for the inclusion of a sufficient number of subjects in the studies, the latter being regarded as the most challenging aspect in performing clinical trials in children (74% and 59% for companies and pediatricians, respectively). An additional complication is the collection of biological samples, especially when these are frequent or invasive.

Methodological aspects are more frequently a matter of concern for the sponsoring companies/CROs, probably because they have regulatory relevance and involve the specific responsibility of the sponsor. Such critical methodological aspects include: getting appropriate patient-derived data, setting validated endpoints that are appropriate for pediatric aims and sample size calculation. Conversely, monitoring and obtaining resources dedicated to the trials, or writing a correct informed consent sheet, are felt to be major hurdles for pediatricians (Figure 1).

When exploring the need of support, as a consequence of the difficulties highlighted, pediatricians seem to be more demanding all across the wide array of items proposed, especially for the practical and administrative aspects encountered in the conduct of a clinical trial, such as "obtaining appropriate insurance," "receiving IRB approval," or having support for the trial monitoring. These outcomes reflect the difference between investigators and sponsors in terms of structure and organization, whereby the availability of dedicated and experienced staff in the companies allows clearance of such problems in a relatively easy way. The recruitment

problem is the only matter of concern that is evenly distributed between companies and pediatricians (as expressed by 44% and 52% of companies and pediatricians, respectively).

Interaction with ethics committees. Ethical aspects are critical especially in child-related research, therefore the interaction with ECs should be easy and supported by mutual trust. In general, the competence of ECs is highly appreciated.

In most cases, the protocol submitted for ethical review is eventually approved by the consulted ECs, however with substantial comments from the ECs in 63% and 45% of instances, as respectively reported by companies and pediatricians, out of the following choices: approval always/in most instances—substantial/frequent comments—frequent rejection. This outcome indicates that the preparation of the study documentation is sometimes insufficient or unclear for a smooth ethics review.

Availability of information and educational activities. In order to improve the awareness of the various aspects of pediatric research, and also to increase skills and competence in the practical aspects of trial conduct, the participation in specific training was felt as useful by most respondents. In fact, the educational support currently available through publications, seminars, trainings, guidelines has been considered inadequate ("less than needed" or "inadequate" amount of informa-

Number of Pediatric Studies					
NUMBER OF STUDIES IN LAST 3 YEARS	0	1 - 2	3 - 5	>5	NO RESPONSE
Companies	25 %	38 %	7 %	5 %	25 %
Pediatricians	13 %	12 %	8 %	11 %	56 %

Source: Kremer, et al.
Table 2. The number of pediatric studies performed in the last three years.

tion, out of a three-level scale: adequate—less than needed—inadequate) by 74% of companies and 69% of pediatricians. Topics most welcomed by companies were those related to compliance issues, enrollment/retention of patients, informed consent preparation and general ethical issues, pharmacokinetics, European Pediatric Regulation, and PIP preparation. Pediatricians have raised the need for advancement in informed consent preparation and general ethical issues, regulatory affairs and European Pediatric Regulation (Figure 2).

Main constraints with clinical trials in children. According to companies' respondents, clinical trials in children find constraints mainly because of recruitment issues

(44%), legislative or administrative issues (30%), and difficulty in obtaining parental consent (30%). Different opinions were expressed by pediatricians, who were most worried by difficulties in obtaining ethics approval (38%), low interest of sponsors (38%), and low financial investments (31%) (Figure 3).

The future of pediatric clinical research. Like the issues described by companies as the main reasons for the slow development of pediatric research, similar concerns are also expected for the future, as being related to recruitment (63%), parental consent (41%), legislation or administrative hurdles (26%), low interest of sponsors (26%), and slow implementation of legislation (22%). Parental consent and recruitment are less frequently mentioned by pediatricians (14% and 10%, respectively), while legislation or administrative hurdles, low interest of sponsors, and slow improvement of legislation are felt by pediatricians as more critical (66%, 55%, and 31%, respectively).

Pediatrician-specific section. The majority of the pediatricians (72%) believe that their therapeutic choices would be better supported by personal updates, based on easy access to the



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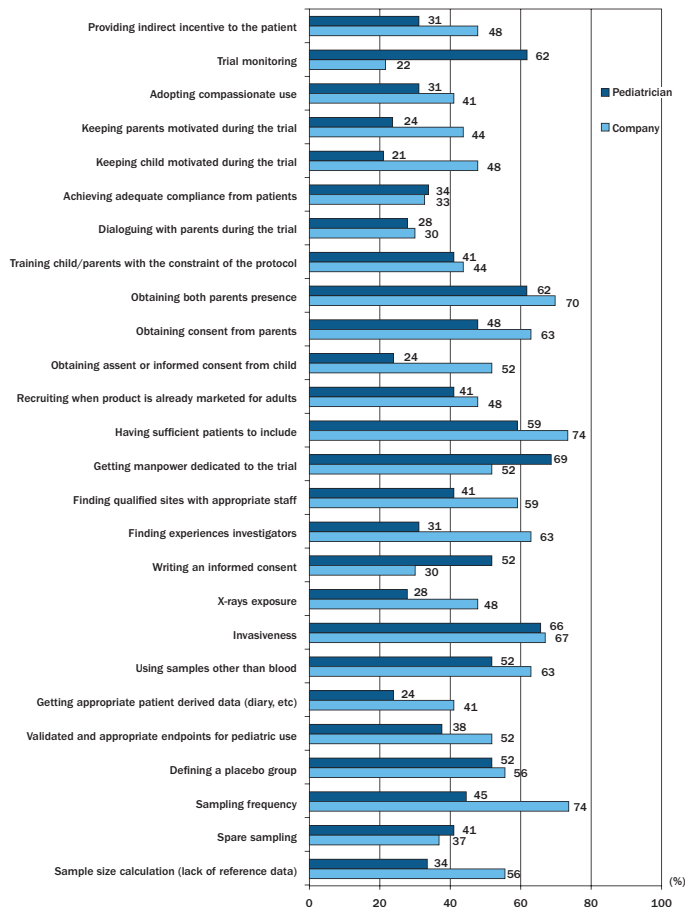
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Main Hurdles Encountered



Source: Kremer, et al.

Figure 1. Main hurdles (“very difficult” or “difficult” tasks) encountered by pediatricians and companies in clinical research with children (multiple choices allowed).

available literature, acquisition of experts’ opinion, or participation in congresses. Personal experience in clinical studies would support 55% of pediatricians in their therapeutic choices (especially by way of randomized clinical trials; much less by way of prospective or retrospective surveys), while the support given by the industry representatives’ for information on therapies is felt to be marginal.

More than a half of pediatricians interviewed (56%) are of the opinion that the medical community has made insufficient collaborative efforts in the development of pediatric drugs.

Company-specific section. Thirty-three percent of companies’ respondents were aware of PIPs submitted by their company. In almost all cases the PIP application was carried out by the headquarters.

Also among respondents from industry, the majority rated efforts made for development of pediatric drugs as insufficient.

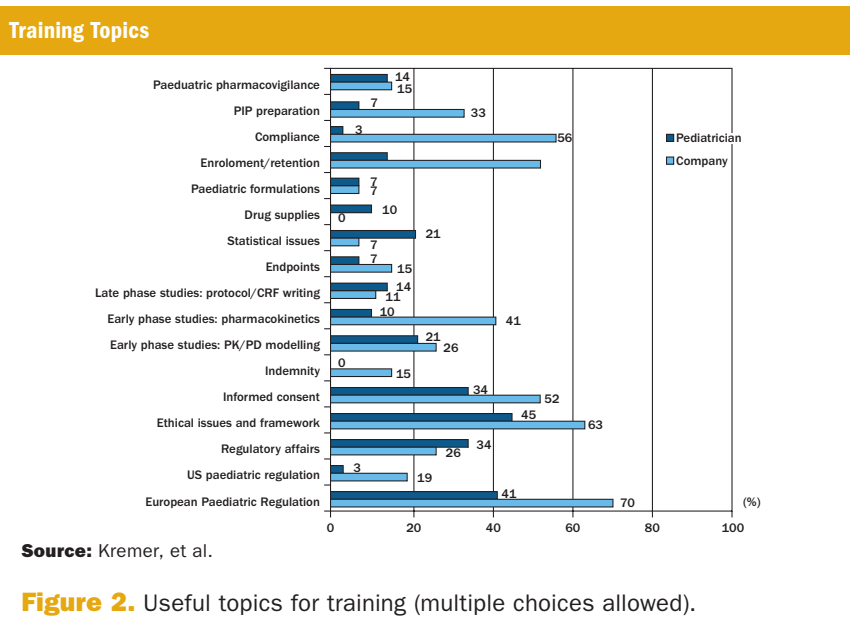
Discussion and conclusions

The results of this survey confirmed some uncertainties still dominating pediatric research among pediatricians, the pharmaceutical/biotech industry, and CROs, as were already highlighted in the previous survey conducted by EUCROF-PWG in 2009. No striking differences can be identified between the outcomes of the two surveys. Most critical difficulties reported in the previous and the current surveys are related to the protocol development, practical issues in the trial management and the need to improve parents’ and patients’ motivation and retention in studies. A need for support in this respect was indicated especially by pediatricians, who have to face the complex organization of a trial in addition to the daily clinical practice, often without dedicated staff. On the other hand, sponsoring companies and CROs need training on the specific regulatory, ethical, and methodological implications of the pediatric clinical development.

It is obvious from these results that the different roles covered by companies sponsoring studies and investigators require mutual support, given the recognized insufficient collaboration among pediatricians and between clinicians and companies. Efforts should therefore be made towards strengthening synergies between the main stakeholders. This interplay should also include ECs, as they represent a major actor in guaranteeing

the safety, rights and well being of children involved in clinical research. Such considerations mirror the results of another previous survey conducted among ECs.⁶

Specific operational, ethical and methodological aspects of pediatric research seem to represent the primary concern, in addition to the increase of the financial burden for the pharmaceutical/biotech industry imposed by the specific pediatric drug developments. Nevertheless, the stimulus given by the Pediatric Regulation to pediatric clinical research is felt as determinant for the availability of drugs specifically designed for children. The perspective of expanding the clinical research in this setting is also welcomed by the pediatric community as a way to increase their experience on specific drugs and on the pediatric clinical trial methodology. The number of pediatric studies newly registered in EudraCT has grown and has reached a level of about 350 per year.⁷ However it is still uncertain whether this will eventually result in

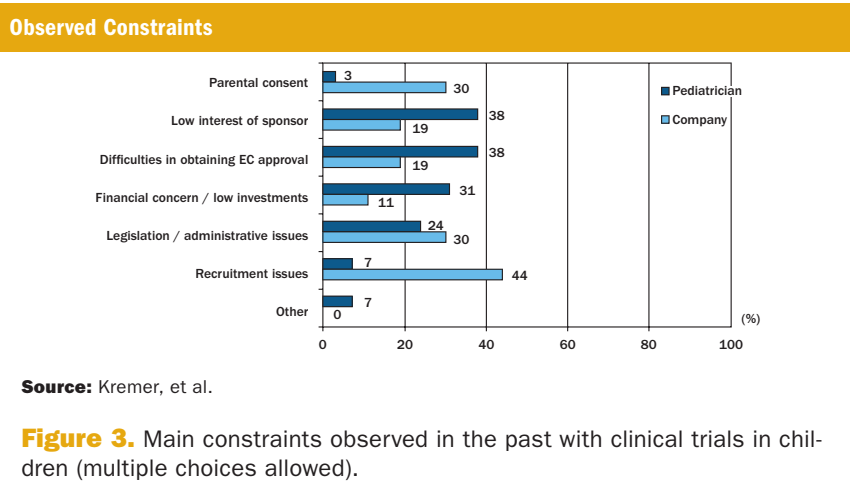


allenges of drug evaluation in children and to protect them from unnecessary exposure to experimental drugs.

*More information on the survey is available in the full article online.

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the desired improvement in the treatment of pediatric population, provided that an improvement all across the organizational, ethical and methodological aspects of pediatric clinical research is needed. This is confirmed by the substantially unchanged perception of difficulties and needs detected in the two EUCROF-PWG surveys.

The results of this questionnaire and also the relatively limited number of responses received may reflect the marginality of pediatric research in Europe. Although such underreporting to the questionnaire represents a limitation of this work, the outcomes of the present survey may represent a basis for further improvement in pediatric research in Europe. One can conclude from the survey that further support should be given to educational initiatives focused on practical issues in the clinical trial management, ethical aspects and new methodological approaches, to overcome the chal-

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Integrating Managed Access Programs: Global Considerations

Simon Estcourt

MAPs can effectively address unmet patient needs and become a cornerstone of product strategy.



For some patients who do not meet the clinical trial enrollment criteria or live outside the region where a clinical trial is being performed, access to a medicine outside the clinical trial setting can represent a new, and in many cases, lifesaving treatment option. Similarly, many drugs commonly available in the United States may have limited availability in foreign markets. Hence, clinicians in these countries are forced to seek untraditional routes to obtain medicines for their patients in need. When such demand arises, implementation of a Managed Access Program (MAP) enables a company to provide treatment options for these patients while not competing with ongoing trials.

While the primary pathway for patient access is through the standard course of drug development, approval, and commercialization, MAPs can generally be considered as an option for enabling early access when the following criteria have been met:

- The primary intent of the MAP is to provide treatment, not assess safety or efficacy
- This is a serious or life threatening disease or condition (based on clinician's medical judgment)
- There are no comparable or satisfactory treatment alternatives available
- The MAP will not interfere with ongoing clinical trials
- The presumed benefit outweighs presumed risk in the context of the disease or condition

Managed access encompasses a variety of regulatory approaches globally including Expanded Access Program, Named Patient Program, Autorisations Temporaires d'Utilisation patient or cohort programs, and Compassionate Use Program. Common to all is the primary objective to provide treatment to patients with unmet medical needs. MAPs can be implemented on a per-patient basis or for a group of patients. This may be desirable in a variety of situations including:

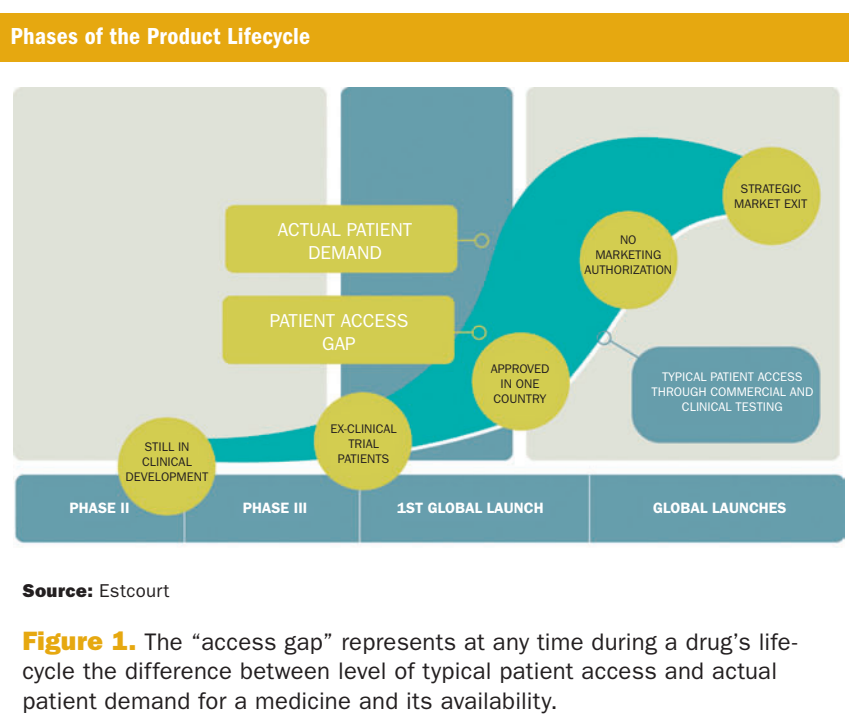
- Medicines that are still in clinical development and may offer a chance for effective treatment, but cannot be accessed through a clinical trial
- To continue treatment between the end of a clinical trial and commercial availability for patients who had been enrolled in the trial
- For medicines that are approved in one country, but not another
- For medicines for which commercial launches are staggered or delayed or may not ever happen in a particular geography
- Where medicines may never be approved, but still offer value for a very small population
- When a medicine is being discontinued from development or commercialization in a specific market or region, but ongoing patients still need treatment

Triggering demand

As a drug progresses through clinical development

and subsequent commercialization, a number of situations can trigger demand for access from patients. Strong positive clinical data presented at a conference may be the subject of media coverage; the drug may be first in class or offer a novel mechanism of action, an improved delivery mechanism or safety profile, or represent a new treatment option for an underserved population, such as in the case of rare diseases. Such demand is typically amplified through social media channels, resulting in an empowered, vocal patient population seeking early access.

Figure 2 shows a representative pattern of patient demand leading up to FDA and EMA approval that was addressed via a recent MAP. In this situation, a large biotechnology company with a diverse pipeline of specialty and orphan drugs had a product in development for an oncology indication. While awaiting US and EU approvals, the company experienced



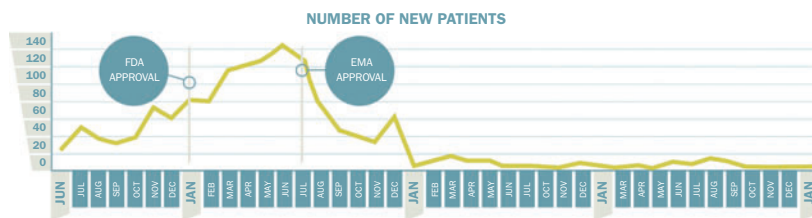
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New Patients



Source: Idis Program Data, November 2012

Figure 2. Number of new patients entering program.

a high level of demand from physicians and patients, which had been generated by heightened awareness of published clinical trial data. The drug represented a major advancement over existing therapies that were currently being used off-label with limited efficacy and significant side effects.

The company put a MAP in place to address this demand. The company chose to partner with a MAP expert so that its internal team focused on US/EU registration activities, approvals and commercial launches.

As shown in Figure 2, the number of patients gaining access to the drug via the MAP grew steadily prior to FDA approval, and continued to climb during the period leading up to EMA approval. Once approved by EMA, new demand through the program tapered off as commercial supply became available. The MAP ultimately delivered product to more than 1,300 patients in 43 countries. Over 950 physicians participated in the program, expanding the real-life experience with the drug among healthcare providers.

Key considerations

Historically, implementation of a MAP has been initiated at the end of the Phase III clinical program or when a drug has been approved in at least one market. Recently, companies have begun MAPs earlier—in some cases as early as Phase II—driven by strong early data and anticipated patient demand. This is particularly apparent in the rare and orphan disease space where treatments have never been available and drug pipelines are limited.

Planning for a MAP should begin six-to-12 months in advance of anticipated demand to allow time for preparation and program development. Consultation with regulatory authorities for approval of the program, and creation of educational information for physicians and pharmacists regarding dosing, administration and restrictions must all be considered in the planning process.

Developing and implementing a MAP also requires the involvement and coordination of many disciplines across the company including clinical operations, medical and regula-

tory affairs, and supply chain/logistics. A cross-functional team is critical to ensure the clinical criteria for patient participation are established, physician educational materials are available, the supply of drug is adequate to support the program, a mechanism is in place to capture all adverse events, and that enrollment in any ongoing clinical trials is not compromised.

Another consideration to make is whether to charge for the drug as part of the MAP. Determining whether or not to charge for the drug in a MAP can be a complicated decision, which should be ad-

ressed on a country-by-country basis before the outset of the program. The decision to provide free access or charge depends on the sponsor's ability to fund a program; the regulations in specific countries; objectives; price; availability of treatment alternatives; and if there is a position on compassionate use.

A company needs to evaluate all of the assumptions and known factors in order to land on the optimal strategy. However, this strategy should allow for flexibility in response to the market dynamics and differences throughout different regions of the world.

If a MAP will be running while registration trials are ongoing, it is important to define the scope of the indication for the MAP and clearly delineate which patients will be included. Companies must define inclusion criteria proactively and objectively to ensure proper selection of patients and identify those who could be moved into the clinical trial population. These criteria must be consistently communicated to all participating physicians. A program run in parallel with a Phase II trial requires more stringency, usually limiting the program to those patients who fall outside the enrollment criteria for the trial, or for patients who cannot gain access to a trial site. Later in the development process, broadening of the criteria for inclusion into the MAP can be considered.

Transitioning trial patients

There are situations in which regulatory authorities require that a trial sponsor continue to make a drug available to trial participants after the study is over until it can be obtained commercially. They recognize the ethical dilemma of withdrawing a drug from trial patients who may be benefiting from an investigational treatment, or not making the treatment available to study subjects who may have received placebo in the clinical trial.

Extending access for study participants via a traditional open-label extension study is one option, but an open-label extension study can add significant costs and require internal resources. Typically, these extension studies continue to monitor patients and collect data similar in nature and frequency to that collected for registration studies, al-

though the return on investment may be limited, based on self-selection and the relatively small number of patients rolling onto the open-label extension study. Compared to open-label extension studies, MAPs generally offer a more economical solution, with less extensive site monitoring, as well as lower investigator fees to participate, depending on the amount of data collected.

Transitioning trial patients from a registration study to a MAP is appropriate when the key rationale includes:

- Provision of treatment as the primary focus
- Interest in continuing access to treatment for patients who demonstrated benefit on therapy during the trial
- Providing a more cost effective and efficient alternative to an open-label extension study
- Rigorous data collection is not a primary requirement
- The additional clinical data collected in an open-label extension study would be of limited scientific value
- The company no longer wishes to develop a product, yet physicians and patients have identified a treatment benefit.

Waiting beyond approval

Despite the marketing approval of a medicine, access may

continue to be delayed for patients in need for a variety of reasons. In these situations, MAPs can provide timely access to much needed medicines.

Figure 3 illustrates the delay in access to treatment that patients in Europe may experience even though a drug has been approved via the centralized procedure. Each year the European Federation of Pharmaceutical Industries and Associations publishes the Patients W.A.I.T. Indicator (Patients Waiting to Access Innovative Medicines). These data represent 66 new medicines available in 2011 that were approved by the EMA during the years 2008 to 2010.

As depicted in the graph, in 19 European countries (excluding the UK), the average elapsed or "wait" time between the date of EMA market authorization and the "accessibility date" (i.e., the date of completion of pricing/reimbursement procedures) varied from 116 to 848 days. The sometimes substantial lag between approval and commercial availability is often the result of national pricing and reimbursement negotiations and a growing trend toward the use of health technology assessments, in addition to national, regional, or local variations.

For each country the blue bar represents the percentage of medicines with a valid EMA marketing authorization

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RARE: The Journey of a Clinical Trial

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When **Donna Appell** learned that her baby daughter Ashley suffered from a rare genetic disorder that would kill her in thirty years, she was told there were less than thirty people in the U.S. who were known to have it and no one knew where they were located.

Realizing that no one was going to help cure "just one child," Donna set about forming an advocacy group using the Internet to gather as many patients as possible who suffered from Hermansky-Pudlak Syndrome (HPS), which includes albinism, blindness, a bleeding disorder and often a fatal pulmonary fibrosis. By the time Ashley turns twenty, Donna has achieved something incredible: the advocacy group she



started is now in the hundreds and the NIH has agreed to start a clinical trial.

like to live with a rare genetic disease, and opening an intimate window into the world of clinical trials.

This session will feature a viewing of *RARE*, and will be followed by a question-and-answer session.

See the *RARE* Trailer from Grainger-Monsen Newham on Vimeo at <http://vimeo.com/24945861>

Filmed with intimate access over three years, as the clock ticks and the stakes get higher, *RARE* follows Donna and her advocacy group in a race to fill a drug trial they hope could prolong her daughter's life. *RARE* takes viewers into the world of what it is

like to live with a rare genetic disease, and opening an intimate window into the world of clinical trials.

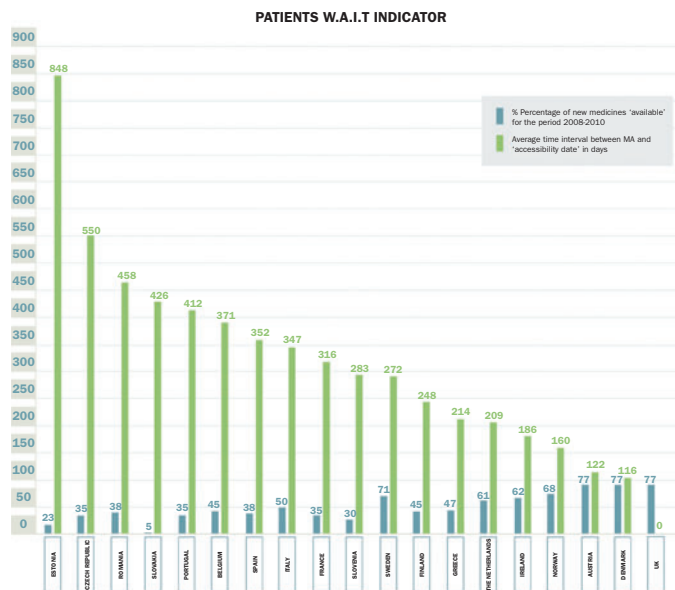
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Time Between Marketing Authorization and Patient Access



2011 Report - Based on ESPRA's database (first EU marketing authorization in the period 2008-10)

Source: Patients W.A.I.T Indicator, European Federation of Pharmaceutical Industries and Associations

Figure 3. Average time interval between marketing authorization and patient access for EMA medicines. Medicines with EU Marketing Authorization from January 2008 to December 2010.

during the previous three years, which were "available" commercially in 2011.

MAPs vs. clinical trials

While clinical trials and MAPs both provide patients with controlled and compliant access to investigational drugs, their approach to doing so is quite different. For example, in a clinical trial setting, regulations take a "top-down" approach in that there is a protocol, stringent rules, and guidelines from which there can be no, or minimal, deviation. With a MAP, the rules and regulations can be described as "bottom-up," i.e., unique to each country or circumstance. Frequently, collection of safety data on the patients receiving drug is the only requirement, making a MAP significantly less costly than a clinical trial. Despite the different approaches, MAPs can work synergistically with clinical trials, addressing the needs of patients who do not fit within the typical clinical framework. Sometimes via a MAP, patients are identified who more appropriately should be treated within a clinical trial, and they are referred into that setting, thereby helping to increase enrollment into registration studies.

Additional benefits of MAPs

In addition to the primary objective of providing access to

patients in need, MAPs offer a number of additional benefits which include:

- Providing treatment without requiring significant supporting infrastructure to be in place in countries where commercial launch is not initially planned or will be delayed
 - Pre-approval use among early adopting clinicians can provide real world information pre-launch that can be used to ensure easier adoption at commercial launch
 - Access is still controlled and once a MAP is in place, patients can receive the medicine they need quickly
 - Feedback from global use can lead to strategic and informed decision making
 - Collection of additional data within the real world setting may increase understanding of how a drug will be used in clinical practice and could uncover patient sub-types not currently in the clinical trial setting
 - Transition of patients to commercial supply can be more organized
- MAPs can address the unmet medical needs of patients when they do not have the ability to obtain medicines

within a clinical trial or through commercial access. In our world of global communication and social media, planning for patient demand is helpful.

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EMA Guidance Points to Central Statistical Monitoring



While capable of conducting high-quality trials, the current oversight process can be expensive and inefficient.

Marc Buyse, ScD
Founder of CluePoints Inc.
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The release of the final version of EMA's Reflection Paper on Risk-Based Quality Management in Clinical Trials marks an important milestone in efforts to introduce and develop the risk-based monitoring paradigm. As data quality is unquestionably what matters most in determining study success and ensuring patient safety, the latest recommendations have created growing demand for practical solutions to simplify the transition to risk-based techniques and help the industry put regulatory advice into practice.

Current quality systems implemented by sponsors and CROs have been widely acknowledged as time-consuming, while commanding a major proportion of the cost of drug development programs. To minimize the pressure on resources, the EMA reflection paper demonstrates the need for a more systematic, prioritized, risk-based approach to quality management that complements existing quality practices, requirements, and standards. The document draws attention to the fact that the ICH GCP guideline was finalized in 1996 when clinical research was largely paper-based. Since then, the industry, the available technology, and the approach to the conduct of trials, have all evolved considerably necessitating that monitoring approaches follow suit.

Much of the industry would agree that while capable of conducting high quality clinical trials, the current oversight process can be expensive and inefficient. Central statistical monitoring (CSM) could provide the ideal answer as it can help alleviate quality management issues by identifying risk and determining the integrity of clinical data throughout the drug development process. The final version of the EMA reflection paper does not differ much from the draft published two years ago, and essentially endorses the use of CSM. The paper highlights the potential to develop central monitoring systems using statistical methodology to monitor the quality of the trial conduct and data. It supports the use of regular metrics reports to demonstrate that checks are being conducted and ensure compliance with pre-defined monitoring strategies. By doing this,

sponsors and CROs will be able to target on-site monitoring visits to address the issues that such visits are better placed to detect.

In light of both the EMA and FDA recommendations, statistical monitoring methods are now proving essential in today's clinical trials. The use of CSM determines the expected values of each variable by examining the data from all investigative sites involved in a trial to identify statistical outliers. Complex and proven statistical algorithms drill down into individual patient data to detect issues that could put a study at risk and create barriers to successful submissions. The approach is based on the actual clinical data and not subjective indicators. The rationale behind this is that all variables are indicative of quality—whether it is lab data, clinical data, baseline data, or treatment outcomes; everything is analyzed and deemed equally important. In a clinical trial, everything that is collected should be worth collecting, and therefore worth checking. CSM determines the quality and integrity of all data and ensures that monitoring efforts focus on errant sites efficiently.

Looking at the CSM method practically, adopting the approach requires minimal work for study teams in gaining objective information and sponsors who strategically outsource to CROs are also finding increased efficiencies by using the method as an oversight tool to regularly check the quality of their data. Implementing these techniques can not only reduce costs and address the latest regulatory guidance, but can make better use of resources and optimize overall trial success rates.

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