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APPLIED CLINICAL TRIALS

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- New Combination Drug Challenges
- Clinical Research Perceptions in Europe
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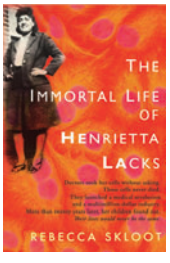
KEYNOTE SPEAKER

BESTSELLING AUTHOR

Rebecca Skloot



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Editorial Offices

485 Route 1 South, Building F, Second Floor, Iselin, NJ 08830 USA
+1 (732) 346-3080 fax: +1 (732) 647-1235, www.appliedclinicaltrialsonline.com
EDITOR-IN-CHIEF **Lisa Henderson**, lhenderson@advanstar.com
MANAGING EDITOR **Michael Christel**, mchristel@advanstar.com
COMMUNITY MANAGER **Hannah Richter**, hrichter@advanstar.com
ART DIRECTOR **Dan Ward**, dward@media.advanstar.com

EUROPEAN EDITOR **Philip Ward**, philipward1@btconnect.com
PO Box 114, Deeside CH5 3ZA, UK +44 1244 538 583

WASHINGTON EDITOR **Jill Wechsler**
+1 (301) 656-4634 fax: +1 (301) 718-4377

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PRODUCTION MANAGER **Karen Lenzen**
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CLINICAL TECHNOLOGY

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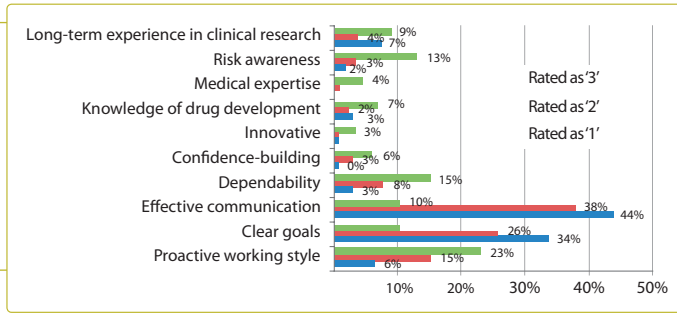

Source: Yakov Datsenko and Johanna Schenk, PPH plus

eLearning

Applied Clinical Trials Online New Look Revealed!

Our efforts to improve our website function and design have arrived. We continue to categorize information to our zones: CRO/Sponsor, Sites, ClinTech, Labs, Regulatory, and Trial Design, but we have also added a section for Project Managers, and links to hot or trending topics, currently Risk-Based Monitoring and Clinical Trials Data Sharing. Go online and learn more about the many resources we offer. www.appliedclinicaltrialsonline.com

Value-Based Auditing of Software Suppliers

Why do we audit our suppliers and what do we hope to achieve when we do? Certainly, regulated companies need to ensure their systems meet both business and regulatory requirements, which include systems provided by third-party suppliers.

To meet the rapidly evolving needs of regulated companies, many technology suppliers have adopted advanced development, implementation, and hosting methods. All too often, however, unprecedented and unfamiliar methodologies leave these same regulated companies unsure of how to audit in a way that is sufficient for purpose and compliant with regulatory expectations and their own procedures. Thus, audit practices need a facelift to keep pace with the technologies that need to be assessed.

In mid-2012, the U.S. Government Accounting Office identified a number of practices and approaches as effective for applying Agile software development methods to IT projects. More recently, in mid-2013, the U.S. Federal Risk and Authorization Management Program approved a cloud technology provider for use in government business. Although these notices are specific to the U.S., it is not a great leap to envision other government entities within the U.S., as well as healthcare regulators worldwide, recognizing the value and necessity of considering new technologies as they look to improve their own operations.

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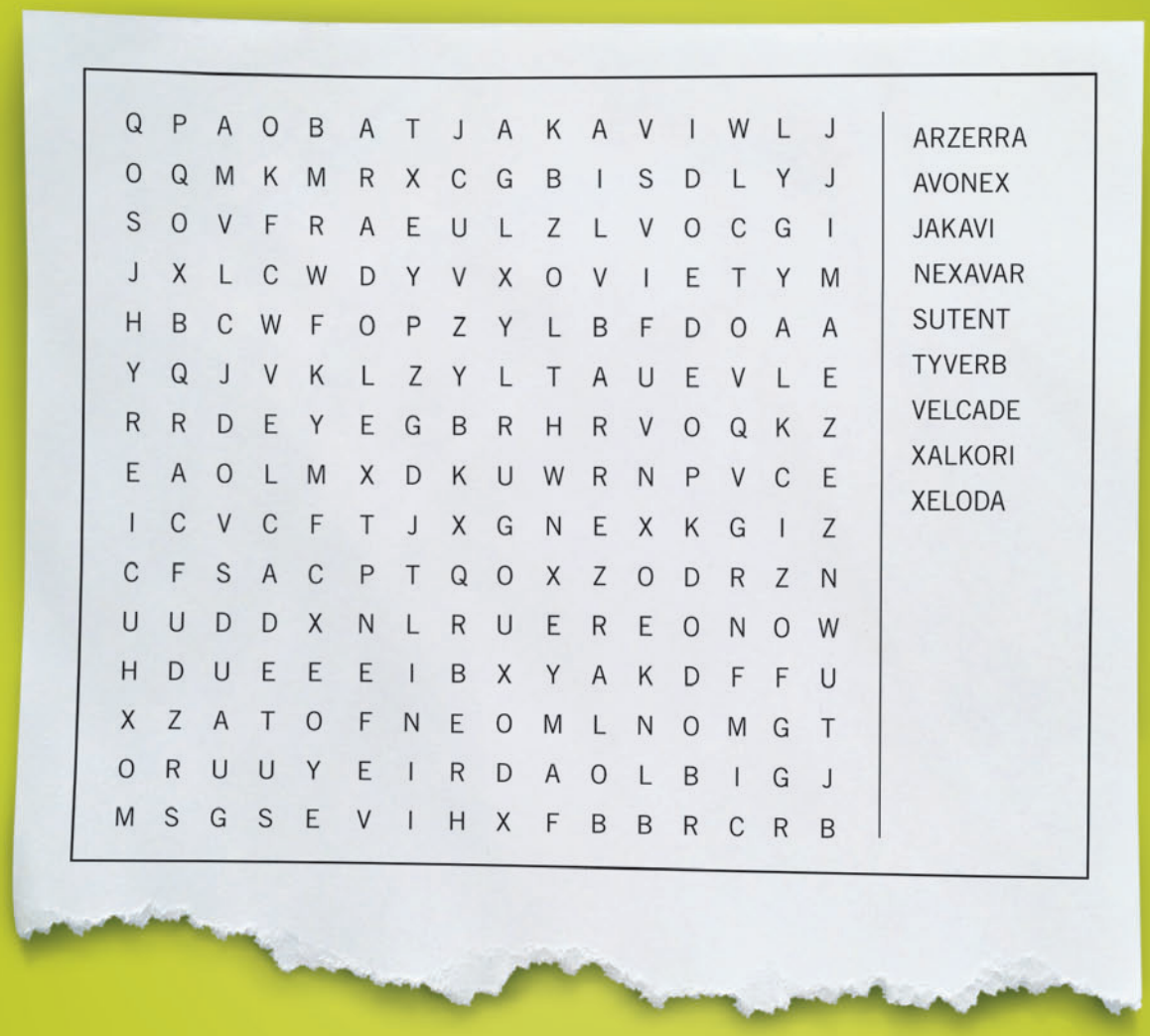

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VIEW FROM WASHINGTON

Sponsors Face New Challenges in Developing Combination Drugs

Virtually all new injectible drugs and biologics are being developed as combination therapies, with special delivery systems designed to ensure proper dosing. An FDA rule issued in January 2013 on manufacturing standards for drug-device combination products indicates that its requirements apply to a wide spectrum of therapies utilizing syringes, patches, pumps, inhalers, nasal vaccines, targeted nanoparticles, and other delivery systems.

The promise is that customized delivery of injectible drugs and biologics will reduce toxicity, enhance individual response, facilitate the delivery of multiple drugs, minimize waste, and encourage patient adherence to prescribed treatment. These features are particularly important for personalized therapies that tend to target small patient populations and seek to justify higher prices based on enhanced value.

Biopharmaceutical companies, thus, are "transitioning overnight" into combination product companies, commented Dave Anderson, associate director for R&D quality at MedImmune/AstraZeneca. This involves developing therapies with devices, packaging, and patient information to meet the needs of prescribers and end users, he explained at an October meeting in Washington, D.C. on combination products sponsored by the Drug Information Association (DIA). Anderson noted that delivery of multiple sclerosis therapy has evolved from using just pre-filled syringes to sophisticated devices that can guide the patient through the injection process in 26 languages, adjust needle speed and depth, and record time of use.

The development of such products often involves expanded preclinical testing programs to include "human factor" testing on whether patients can use a device delivery system appropriately. Manufacturing controls and quality systems vary considerably for drug and device components, as does product labeling and post-marketing requirements.

A first step in combination product development is to determine whether it should be regulated as a drug, biologic, or device, based on primary mode of action. For uncertain or complex situations, sponsors may consult FDA's Office of Combination Products (OCP), which will decide if a product is a combination and which FDA center should oversee its development program and market approval. OCP received over 800 requests for consultations in fiscal year 2013, and 330 combination product submissions were filed during that same period, with the drug the main component in 153 cases. FDA Centers and sponsors also sought assistance from OCP in resolving nearly 400 regulatory and development issues involving requirements for clinical and preclinical testing, registration, and regulatory issues.

A range of industry collaborative models support combination product development, explained Pfizer senior director Kristen Paulsen at the DIA conference. She noted that it is important to decide very early in development what human factors studies are needed to avoid problems in Phase III trials, and to clarify responsibilities for such issues as who is responsible for shipping devices to sites and at what study phase to test the drug and device in combination. Sponsors need to file only one application to begin clinical trials for a combination product, noted OCP deputy director Patricia Love. If the Center for Drug Evaluation and Research (CDER) is the lead, the program follows CDER policies and meeting process, with participation from OCP and other relevant Centers.

Regulatory confusion

FDA's stated aim in issuing its January 2013 final rule on current good manufacturing practices (cGMPs) for combination products is to encourage innovation by streamlining the regulatory process for ensuring compliance with manufacturing standards. The rule seeks to avoid duplicative requirements by establishing either drug GMPs or device quality systems as a foundation, and incorporating provisions from other Centers as appropriate. This approach applies to co-packaged and single-entity combos, but not to vaccines, cellular therapies, and other products regulated by the Center for Biologics Evaluation and Research (CBER).

Yet FDA also indicates that design controls for devices and release requirements for drugs apply to the whole combination product, which has generated confusion over the "streamlining" process. An added problem is how manufacturers should deal with legacy combination products, which often have gaps in now-required development and production records. FDA is receiving many questions on the GMP rule and planned to address them in draft guidance, promised for 2014. Industry concerns have escalated since FDA issued a warning letter to Amgen in January 2014 citing inadequate design validation, documentation of product changes, and contractor controls for certain therapies the agency defines as combination products.

At the same time, a revision of medical device regulations by European regulatory authorities is expected to impact development and authorization of combination products. Drugs and medical devices are regulated very differently in the EU, which lacks a specific program for overseeing combination products, as in the U.S. The development of more drugs with customized delivery systems, though, has brought to the fore multiple "borderline issues" involving EU oversight and authorization of these products.

— Jill Wechsler

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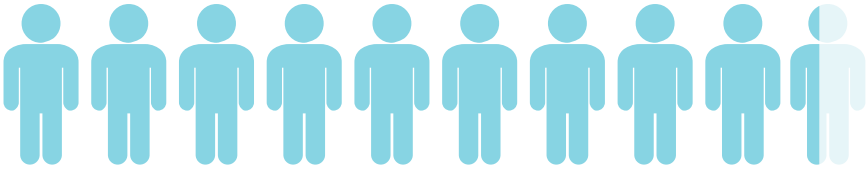

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VIEW FROM BRUSSELS

Health Challenges Mount for Europe

Region is facing a widening range of problems as the EU tackles external threats and internal changes

Top of the news—even for a column that appears with a schedule only tenuously related to a news agenda—has to be the untimely and unfortunate removal of Guido Rasi from his post as executive director of the European Medicines Agency (EMA), as the consequence of an absurd error in the appointment procedure. But at this stage, that news can be little more than a lament. In a health policy world where competition for profile is tough, a vacuum at the top is a serious disadvantage. Until a successor is appointed, the agency is inevitably going to be limited to business as usual—of which there is plenty, but there was plenty more to be done on forward thinking that will now be put on hold. As soon as the situation becomes clearer on who will take over at the head of the EMA, this column will return to exploring options for the new executive director, and for the agency itself.

The new health commissioner

Meanwhile, to a new appointment that also has major significance for the world of health in general, and clinical trials in particular, and where we do know who is taking on the job. European Commissioner for Health and Food Safety Vytenis Andriukaitis has now been anointed, and will be one of the key influences on health legislation over the next five years. His appointment follows his gaining the backing of the members of the European Parliament (MEPs) who auditioned him for the job in October. In his audition, he offered some clues as to his approach, and articulated them in a number of commitments. Those MEPs are determined to hold him to his word. So much so that they have listed the commitments in a formal document, quoting verbatim Andriukaitis' observations to the parliament.

So we can now look forward to what he may do with public health systems reform. "I plan to continue work to assess the performance of health systems and underpinning advice on healthcare systems reform," he said. And in response to population ageing and the growing burden of chronic diseases, "I will support efforts to make health systems more efficient and innovative; so that they can provide equitable healthcare to all citizens, while remaining financially sustainable." On primary care and e-health, "I will work on universal health coverage, strengthening primary care, improving quality and safety, promoting e-health." In support of prevention and healthy lives, "I intend to put much focus on enhancing prevention." On bridging inequalities in health, "I will seek to ensure that every initiative on health contributes to bridging the wide inequalities in health that persist in Europe."

On his role in enforcing health legislation, he indicated his determination to push forward the follow-up of the recent European Union directive on patients' rights in cross-border healthcare. This is designed to allow a form of health tourism, in which EU citizens can not only go to other EU countries to be treated, but can expect to be reimbursed for their care. This is also the legislative measure which has provided the first legal base for the EU to work on health technology assessment and on e-health.

The Ebola challenge

Andriukaitis said that he would "also work with member states to protect citizens against any cross-border health threat, with an immediate focus on the Ebola outbreak in West Africa." That challenge has grown in significance even since he made the commitment, as the number of deaths in Africa has risen, and as more health workers have returned from the region to be treated for infection. In fact, Andriukaitis' first trip since he took on the job was to Guinea, Sierra Leone, and Liberia, to make an on-the-spot evaluation of the nature of that challenge.

His focus chimes with the EU's broader efforts to boost the developed world response to the Ebola challenge. Already the European Council has appointed the new commissioner for humanitarian aid, Christos Stylianides, as the coordinator of the EU response, and the EU and its member states have made more than $1 billion available for short- and medium-term efforts. New money has been put into developing new vaccines and treatments, including some $300 million for a joint EU-pharmaceutical industry initiative to boost research into Ebola vaccines and protocols for hospital-infection control. At the same time, preparations are now underway to start clinical trials for new treatments for Ebola at three sites in West Africa. The trials, run in partnership with Médécins sans Frontières (MSF), could yield initial results in early 2015.

Meanwhile, the new health commissioner will have to make progress with ensuring that EU legislation on clinical trials and counterfeiting and pharmacovigilance and a host of other matters is satisfactorily put into effect across the EU, as well as advance a series of strategic discussions on how to make health systems in Europe sustainable while fostering innovation.

— *Peter O'Donnell*

GLOBAL REPORT

DIA Opts for Paris in the Springtime

Ella Fitzgerald always loved Paris in the springtime, and the Drug Information Association (DIA) is now hoping the French capital will prove to be an irresistible lure for the pharmaceutical industry. For the 27th DIA Annual EuroMeeting, organizers have switched the event from its usual late March slot to mid-April in 2015.

The congress will look at some of the major challenges facing global health today, including the need to come together to drive innovation. The opportunity of the Innovative Medicines Initiatives (IMI) and other public-private partnerships are formative mechanisms that must be maximized in Europe and other regions, program chairs note.

Discussion at the meeting will concentrate on how early and harmonized regulatory dialogue is necessary to ensure clinical development that is more efficient and will accelerate access to novel therapies for patients. The role of the European Union's new clinical trials legislation will come under scrutiny in the meeting's opening track on access to innovative treatments.

Another track will look at special development pathways in pediatrics, the elderly, and in pregnancy. Nearly 10 years after the adoption of the Paediatric Regulation, substantial experience has been gained, yet science continues to evolve in this area and raises new questions to be answered in the future. At the same time, the need for global convergence has become evident in several areas. Also, the speed of traditional development concepts is slower than the speed of ageing in European society, according to the theme leaders.

Further parallel sessions will focus on innovation in vaccine development, medical devices, and combination products, novel treatments for rare diseases, availability of medicinal products/drug shortages, pharmacovigilance, big data, and mobile health, among other areas.

Paris has a rich history of medical innovation. Local scientists and clinicians have changed modern medicine through the discovery of instruments such as the stethoscope and hypodermic needle, treatments like antibiotics or antipsychotics, vaccines against tuberculosis and rabies, and the discovery of diseases such as HIV.

—*Philip Ward*

DATA ANALYSIS

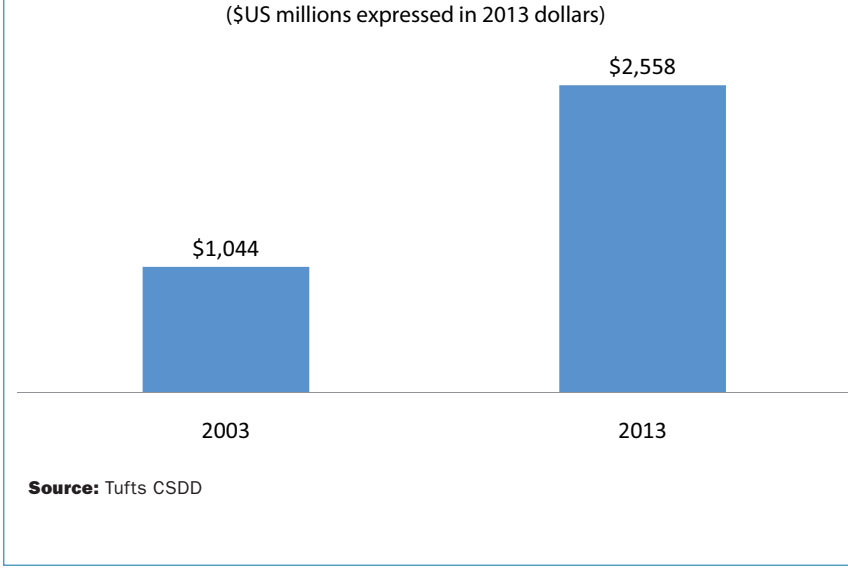
The Cost to Develop an Approved New Drug Now Exceeds $2.5B

Based on a recently completed analysis, the Tufts Center for the Study of Drug Development (Tufts CSDD) estimates that the cost to develop a new prescription medicine that gains marketing approval is now $2.6 billion. This figure includes $1.4 billion in direct out-of-pocket costs to develop the new prescription drug, plus the high cost of drug failures and the capitalized costs spent over a lengthy drug development cycle time.

The estimated cost to develop an approved drug in 2003 is $1.04 billion (expressed in 2013 dollars). The updated $2.6 billion cost estimate represents an 8.5% compound annual growth rate over the 2003 level. Factors that have likely contributed to this high and rising cost to develop an approved drug include larger and more complex clinical trials and declining drug development success rates.

— *Tufts* CSDD

The Price of Innovation



Source: Tufts CSDD

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Education and Satisfaction Disparities Evident Among European Patients, Public

Study spotlights the challenges and opportunities to better engage the patient community in Europe

Good news: recent research among a global public and patient community shows general improvement in attitudes and perceptions about clinical research. Bad news: there is one group—patients and the public in Europe—with consistently more negative opinions and views that appear to be getting worse.

Based on nearly 850 responses, a recent Center for Information & Study on Clinical Research Participation (CISCRP) study finds that the European public considers clinical research to be riskier than does the public in many other global regions. Moreover, the European community shows the lowest self-assessed general knowledge about the clinical research process and the lowest level of willingness to participate in clinical trials. Among European study participants, a higher percentage finds the informed consent form review difficult to understand relative to their geographic counterparts. And study participants in this community are among those least willing to consider participating in another clinical research study.

Although we can speculate, the root causes of the problem are not completely clear. A closer look at the attitudes and perceptions in this particular community strongly indicate that much more focus and attention is required to address underlying concerns and implement targeted outreach, education, and new patient engagement initiatives.

Perceptions & insights

Between January and March 2013, CISCRP—an independent non-profit organization—developed and conducted the "Perceptions & Insights Study" to resume and establish routine global assessment of public and patient perceptions, motivations, and experiences with clinical research participation. The online study was conducted among a global community of health information seekers and research participants. A total of 5,701 international respondents completed the survey, making it one of the largest international clinical research surveys ever conducted. Given the sample size, generally a three to five percentage point difference between subgroup values is significant at the $p<.05$ level.

To reach a global community of respondents, CISCRP collaborated with Acurian (now part of PPD), a worldwide provider of patient recruitment and retention services—for its help in reaching and engaging respondents. 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.

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

The highest concentration (75%) of respondents resides in North America; 15% are based in Europe, 5% from South America, and another 5% from Asia-Pacific. A majority of respondents (58%) are female. Approximately four out of 10 respondents in Europe and in North America had participated in a clinical trial prior to completing the online survey. Respondents diagnosed with an illness represented a broad mix of disease indications.

Higher perceived risk

One out of five people overall considers their general knowledge about clinical research to be poor, but there is wide variation by geographic region. A significantly higher proportion of the public in the Asia-Pacific and South American regions views themselves as less informed, with 28% and 31%, respectively, doing so. But the European public considers themselves to be the least informed, with nearly half (47%) indicating so.

The European public views clinical research as riskier than do their North American counterparts. Approximately one in 10 people in North America believe that clinical research studies are "not at all" and "not very'" safe. This compares with nearly twice that rate (18%) of the European public.

Almost 60% of the public in North America and 53% of those in Europe share the view that the possibility of experiencing side effects is high while participating in a clinical study. A much larger proportion (27%) of the European public believes

that study participation poses risks to one's overall health compared to approximately 20% of the public in each of the other global regions assessed.

General public willingness to participate in a clinical research study is consistent with that seen in past global surveys. At this time, a very high proportion (87%) of the public says that it is "somewhat willing" and "very willing" to participate in a clinical research study. The European public shows the lowest level of willingness to participate, with only 58% indicating so in 2013. This compares with 66% of the South American, 73% of the Asia-Pacific, and 90% of the North American public. A lower proportion of the public in Europe is willing to participate in clinical research today than did so in 2007 (71%).

Harder informed consent, lower satisfaction

Among all respondents, one-out-of-five study participants consider the informed consent form to be "somewhat difficult" or "very difficult" to understand. But wide differences are observed by global region: a much higher proportion in Europe—four out of 10 study participants or twice the overall rate—found the informed consent form difficult to understand. In this one regard, study volunteers in South America and Asia-Pacific had the hardest time understanding the informed consent form, with 63% and 69%, respectively, rating their informed consent forms "somewhat" and "very difficult."

Overall, nearly 60% of study volunteers report taking time to read the informed consent form by themselves. A significantly lower percentage of study volunteers outside North America—30% of South American, 46% of European, and 23% of Asia-Pacific—report doing so. Approximately one in four study volunteers read the informed consent form with study staff; the highest percentage (50%) reviews the form with study coordinators. 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).

Among all survey respondents, 85% of study participants 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 European study volunteers is not satisfied that their questions were answered during the informed consent review process.

Lastly, in the aggregate, the overwhelming majority (95%) of study volunteers say that they would consider participating in another clinical research study in the future. The percentage willing to participate has increased by 10% since 2007. But a significantly lower proportion of European study volunteers (80%) share the sentiment. Having been through the clinical trial participation experience, compared with those in other global regions, European study volunteers are among the least likely to participate in another study in the future.

A targeted response

These results, and many more found in the 2013 CISCRP "Perceptions & Insights Study," indicate that there is an urgent need and a major opportunity to educate and engage the European public, patient, and study volunteer communities. There are unique cultural and societal factors contributing to these conditions in Europe. Broad exposure to highly visible and tragic patient deaths in Europe associated with clinical research studies in the not-so-distant-past, and the aftermath of these events, have shaped public attitudes and perceptions.

For a variety of reasons, European public attitudes and perceptions have not rebounded during the past seven to 10 years as have those among the North American public. This may be a function of more frequent and active public outreach and education in North America. Clinical research professional awareness of—and the desire to execute—practices and initiatives that enhance study volunteer experience and establish higher levels of engagement may be relatively lower in Europe at this time.

The efforts of The European Patients' Academy on Therapeutic Innovation (EUPATI)—a consortium funded by the Innovative Medicines Initiative—are much needed to help address the educational disparities among patients and study volunteers in Europe. CISCRP has also turned its sights on the European community with a planned launch of its AWARE-for-ALL public awareness and outreach live event in London in spring 2015. CISCRP hopes to spread its programs and initiatives across all of Europe during the next several years. The European Medicines Agency's (EMA) commitment to improve disclosure and transparency—most notably the distribution of lay language risk-management plans and clinical trial results summaries—will help improve public trust and position Europe as the global leader on this front.

CISCRP hopes to assist the clinical research enterprise in monitoring trends and identifying opportunities to better inform and engage the public and patients as stakeholders and partners. In early 2015, CISCRP will be launching its second "Perceptions & Insights Study," with an eye toward increasing the number of respondents from Europe and other parts of the world.

The Future of ePRO Platforms

Alan Yeomans

The practicality and benefits of using a subject's own mobile device to collect patient-reported outcomes.

It is tempting to imagine the use of the patient's own mobile computing platform for collection of patient-reported outcomes (PROs). This would solve some of the problems faced when using the electronic PRO (ePRO) devices employed today:

- Provisioning costs (purchasing or leasing the devices to be used in the trial)
- Supply issues (delivering the devices to the sites for distribution to subjects, and collection after the subject completes the trial)
- Training (handling and use of the device by subjects and site staff)
- Maintenance and Help Desk (device-related help desk questions, replacement of faulty devices)

This article evaluates the practicality of such an approach, and the issues that need to be addressed if it is to succeed.

Present state of the art

The goal of a PRO system is to collect data directly from subjects; data used to measure the benefit of treatment or the risk in medical clinical trials.[1] Initially, this was done using a pen and paper, and patient responses were collected in the form of surveys conducted once (or a few times) during a trial and/or in the form of a patient diary, containing responses collected regularly throughout the trial.

The move toward ePRO solutions, which started in the 1990s, was fueled by a number of considerations, primarily:

- Improved compliance through the use of alarms, reminders, and date and time stamps
- Improved data quality through the use of electronic data collection and in-built data checks
- Reduced trial times due to quick access to data without requiring data transcription

Interestingly enough, cost has not been one of the primary movers. Although most companies adopting ePRO have had hopes that improved compliance, data quality, and reduced trial times in themselves would lead to cost savings, these are cost savings that are difficult to quantify. Indeed, often the move to ePRO involved higher up-front costs, with eventual savings being realized later in the trial process.

ePRO solutions diverged early along two paths. The simplest and most cost-effective tools have been the interactive voice response systems (IVRS), but these have had restrictions in their functionality, the user interface, and the type of data that can be collected.

In order to support the collection of more complicated data, a number of vendors developed solutions that could support entry of textual and graphical data.[2] These solutions were based on proprietary software running on commercially available electronic platforms, or "device-based applications." Initially, these solutions were based on commercially available personal digital assistants (PDA) platforms. The earliest were based on the Apple Newton PDA, followed in the late 1990s by systems using the Palm Pilot. These all used offline synchronization techniques, making it necessary to store data temporarily on the device itself, initially until the next time the patient visited the clinic. Later on, solutions were developed that allowed subjects to synchronize remotely (e.g., from home). GSM-enabled PDA devices were introduced in the early 2000s, allowing continuous synchronization (as long as the subject was within reach of a GSM network).

The one thing in common for device-based applications is that they used proprietary software in-

stalled on a commercial platform. This necessitated supplying subjects with the devices to be used for the study in question, training them in the use of the devices, and collecting the devices from the subjects as they complete or withdraw from the trial.

Because device-based applications store the application itself and in many cases act as a temporary store for the data then there are special requirements that need to be addressed by these solutions.[1,3] The software must prevent end users from:

- Modifying the application or the data stored on the device
- Installing and using other applications that may influence the device-based ePRO application or the data collected by it
- Deleting the ePRO application and using the device for other purposes

The device-based applications often use hardware specific capabilities in order to fulfill the above requirements, which results in new aspects that need to be considered:

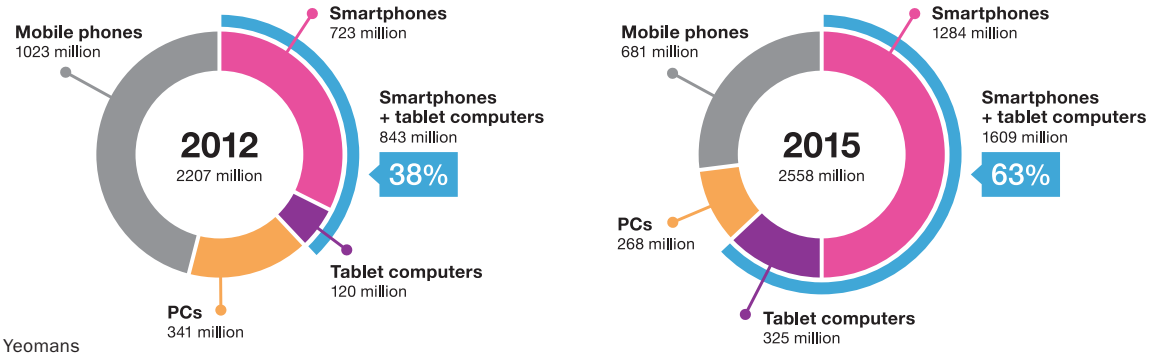
- The ePRO software can only be used on hardware platforms that support the capabilities used[1,3]
- Every release of the device-based application needs to be validated with every release of the hardware it is used on to ensure that the software operates as required (e.g., the user is still blocked from deleting data on the device)[1,3]

PRO instruments and requirements

A PRO instrument is the collection of questions and scales used to elicit information from the subject. It is not dependent on technology as such—a PRO instrument can be implemented on paper, using an ePRO solution or both. However, there is a regulatory requirement that the PRO instrument be shown to measure the correct information to support later uses of the PRO data, for example, in labeling claims. Typically this is shown by validating the PRO instrument.[1,3,4]

One concern has been that a PRO instrument that has been validated in one implementation (usually on paper) may not produce the same results if it is transferred to a new medium (such as ePRO). The concern has been that differences in layout, the presentation of the question, the number of questions presented at the same time, and the size of scales and other similar aspects could influence patient responses. One large study (looking at 46 trials and 278 scales) was carried out to investigate these concerns.[5] The conclusions reached were that the responses collected from the subjects were comparable even when using different media (paper, ePRO). Other similar studies[6,7] have shown that minor changes caused by changing from one media or device to another did not adversely affect the results, but larger variations in the presentation, such as rewording or reordering the instrument, could result in the results not being comparable.

Mobile Momentum



Source: Yeomans

Figure 1. Comparing worldwide mobile platform market shares in 2012 versus estimates for 2015.

New technology

We now have a potential pool of subjects for clinical trials to whom the use of web-based software and mobile computing platforms is commonplace. Web-based applications are now to be found in most users' Internet histories—buying goods and services online, social media, and personal banking are web-based services now used by most of us.

Connectivity and computing power are areas that have seen a dramatic development and evolution in the last five to 10 years. Smartphones and tablet computers that are more powerful than the desktop computers we used just a few years ago are gaining market shares. According to reports from Gartner[8] and Statista,[9] worldwide smartphone sales in 2012 amounted to a little more than 722 million units, of a total 1.746 billion mobile phones sold. In 2013, smartphones were projected to account for 958 million of a total of 1.8 billion mobile phones sold. In addition, by 2015, tablet computer sales are estimated to reach 325 million, while PC sales continue to decline (see Figure 1).

As these trends show, more subjects recruited for clinical trials will have advanced mobile computing platforms, platforms that are more advanced than today's ePRO devices. The standardized delivery of software installed on the client platform (computer, smartphone, or tablet) has also been revolutionized by the use of "apps," which are now even used to install software on other consumer products such as Smart TVs. This enables the easy delivery (over the Internet) and installation of proprietary software on the consumer's own device.

App or web-based application?

What are the advantages and disadvantages of the two new technology solutions that offer us the possibility of using the patient's own device—web-based applications and apps?

Validation

A web-based application requires validation for every supported combination of operating system (i.e., iOS, Android, Windows) and browser (i.e., Safari, Chrome, Internet Explorer, etc.). There is little or no requirement for device-specific validation.

When using apps, there are still some differences between platforms and devices. The user does not have to look far to find examples of apps that run on some phones and tablets but not on others.[10] Hence, the introduction of the "app" methodology has helped standardize the software environment, but the basic validation requirement is still the same—the instrument must be validated on every type of mobile phone, tablet, and computer used in the trial.

Offline

The greatest single disadvantage of a web-based application is that you must have Internet connectivity in order to use it. The latest HTML standard (HTML 5) has introduced limited offline capabilities, but you still need an Internet connection to submit and store the data once the questionnaire has been completed.

The use of a local app allows for local storage of data and synchronization with a central database at a later time when connectivity is re-established. This is a well-established method used by existing legacy solutions and accepted by the regulatory authorities. The only major risk (which is the same for existing legacy solutions) is the risk of losing data if the device is lost or if it should break down.

Installation

A web-based application has a zero footprint on the patient device and no need for local installation on the patient device.

A local app does require installation, and although modern systems (iOS, Android, and Windows) have simplified the downloading and installation of apps, it still must be done. And this also brings into play a range of requirements mentioned earlier regarding device-based applications:

- The need to prevent patients from modifying the app or the data stored on the device
- The need to prevent patients from installing and using other apps that may influence the ePRO app or the data collected.
- The need to prevent patients from deleting the ePRO app

A web-based application simplifies the use of ePRO instruments in all cases except when an offline capability is of vital importance to the trial. Although the use of an app simplifies the

distribution and installation of software and can help ensure that the ePRO instrument looks the same on all supported devices, it does not address the other issues facing the legacy device-based applications, as an app is after all still basically a device-based application.

The use of app technology is an improvement on the existing legacy device-based applications, but it is not a radically new idea—it is simply a standardized environment for the distribution of, installation of, and the operating system for computer software. It is a step toward the future in software development in general that started with the use of Linux (which also delivers all three of those benefits, although the use of Linux is limited for mobile computing platforms).

The future of ePRO platforms can be even brighter when considering web-based applications.

The issues

We want to collect PROs in a fashion that ensures the data collected is correct, dependable, and repeatable, in terms of both:

- Producing comparable responses from the same subject over time
- Producing data that is comparable between subjects

There are a number of challenges to be faced if we want to use the possibilities presented to us by the spread of smartphones and tablet computers.

One of the most important issues is that of validation of the PRO instrument. Attempts to use the subject's own mobile phone for ePRO have often been rejected due to problems with validation of the PRO instrument. The arguments used include:

- How does the sponsor show that the data collected supports their claims, when subjects are using different devices, with different sized screens and varying graphical interfaces?
- How can they ensure that the results are comparable except through validation of the instrument on every type of mobile phone used in the trial?

The cost of such a validation effort is prohibitive.

The solution

The studies mentioned earlier[5,6,7] give a clue to how such a situation can be handled. Their findings indicated that minor changes in appearance of the PRO instrument still produced comparable results. This can be leveraged by ensuring that:

1. Devices with comparable capabilities are used. Smart phones and mini-tablets all have similar sized screens, similar graphic resolutions, and similar colors.

2. The PRO instrument needs to utilize a common graphical denominator that appears the same on all devices (e.g., all answer choices are shown without scrolling). When using larger tablet computers and PCs, then the same limited area should be used for display as on smart phones and mini-tablets.

3. The use of a single application across all devices ensures the same "look-and-feel" within the PRO instrument with regards to ordering and presentation.

4. The use of a web-based application would mean there was no software installation required on the subject device.

5. The use of a web-based application counteracts the need for computer system validation on each possible platform.

The study protocol and the design of the PRO instrument should take into account the need for comparability in responses across slightly different devices, and, thus, avoid cases that could potentially create difficulties. The use of advanced graphical scales, such as graphical body representations (e.g., point at the part of your body that is in pain) is generally considered to be more dependent on exact equivalence in the graphical representation than textual questions and answers. To ensure compliance across multiple devices, the body could be divided up into different areas (head, shoulder, etc.) that are highlighted if the subject clicks on any part of that area.

How many of the prospective subjects in our clinical trials have their own smartphones? Market analysts predicted[11,12] that the major pharmaceutical markets will pass 50% market penetration for smartphones from 2012 to 2014. If a subject group contains subjects that do not own a device suitable for use in the trial, then a mixed model can be used. The advantage of a "subject's own device" model is that it implicitly allows for varying devices to be used in the same trial. One advantage is that even

if a subject changes device in mid-trial (e.g., purchases a new smartphone), then data compliance is still maintained.

Regulatory aspects

It is absolutely essential that any system used to collect data for clinical research is compliant with the regulations and guidelines covering this work. So when evaluating the use of new technology, it is especially important to highlight the areas that differ from existing solutions, and whether these areas require special consideration in order to ensure regulatory compliance.

The use of a web-based software application instead of a device-based application does not alter the fact that the software used needs to be documented and validated in exactly the same way as all software in the industry is handled. It is also the responsibility of the investigator and trial sponsor to formally document a risk assessment (Quality Risk Management Plan) for the continuity of data entry when a subject loses his or her device or decides to get a new one. This already applies even when using legacy device-based applications, hence, there are no extra burdens when moving to a solution based on the patient's own mobile computing platform.

When using a legacy device-based application, it is vital that the user cannot influence either the application or the data stored locally. An important functionality (and validation step) to be considered when developing device-based applications is how to disable user access to the software and data, and validating that there is no way the user can get at the software or data.

The following problems when using device-based applications are automatically solved by the use of a web-based application:

- Loss of data due to loss of device or device malfunction
- Collection of incorrect data due to the latest protocol amendment not being implemented on the device

The solution of these issues for device-based applications involves additional software, and, therefore, additional validation effort and additional risk.

Using the patient's own mobile computing platform provides substantial savings from a regulatory compliance point of view. There is no software installed on the remote device, nor is any data stored. Therefore, the fact that the patient's own device is being used becomes almost unimportant—as long as it supports the web-based application, no further validation is required. Platform support can be programmed into the web-based application itself in the form of requiring certain versions of given browsers; if they are available on the patient's device, then there is no problem. The use of the patient's own device then becomes directly analogous to the use of a telephone in an IVRS system—there are no requirements to validate IVRS systems against all possible telephones in all countries in the world; it is enough that standard telephone functionality is available to the subject.

Summary

What are the advantages that a subject's own device solution offers? The major advantages were named in the opening paragraph, namely provisioning, supply, training, and maintenance. When would the legacy IVRS and device-based applications be more suitable? IVRS solutions do not require a mobile computing platform; they operate on any telephone. In this respect, they are still applicable for all potential subjects that have access to a telephone, but not to a smartphone, tablet computer, or PC. This is currently a large, but diminishing, proportion of the overall pool of subjects. Device-based applications can still be the solution of choice for trials with specific requirements for a uniform hardware solution. One example is a requirement to connect to external equipment at the subject's residence, such as PEF meters and blood pressure cuffs.

The future is already here

It would appear that there are few, if any, insurmountable problems with the use of the subject's own device. If the study protocol and the PRO instrument have been designed with this in mind, then the ePRO comparative studies already conducted[1,6,7] indicate that the subject's own device can be used.

Traditionally, large corporations in the clinical research sector exhibit a certain resistance to adopting new technologies, but are there any regulatory or other substantial concerns that would contraindicate adopting the patient's own mobile computing platform for ePRO? As can be seen from the previous summary, the answer is no.

So why isn't this already being done? Actually, it is—all around the world, trials are presently being run that collect ePRO data in this fashion, including studies critical to regulatory submissions. The FDA[1] and the European Medicines Agency (EMA)[4] have issued guidelines and reflection papers, which outline their current thinking when it comes to compliant use of ePRO.

Examples of studies using a web-based application on the patient's own mobile computing platform include:

- A Phase II clinical trial in the U.S. testing the use of a new pharmaceutical designed to increase sexual desire, arousal, and satisfaction in females with sexual desire disorder. The ePRO data contains primary efficacy data as the measure of success of the treatment and is heavily dependent on the qualitative responses from the subjects. The trial included more than 200 subjects at more than 15 sites in the U.S.
- A medical device trial in Europe to evaluate an additive for pain relief in a plastic surgery product used for cheek shaping. Again, the ePRO data containing primary efficacy data as the measure of the degree of pain relief is heavily dependent on the qualitative responses from the subjects. The trial included more than 50 patients at three sites.
- An investigator-initiated Phase IV trial in Japan to test the efficacy and safety of three types of hyaluronic acid injections into patients with osteoarthritis of the knee. The ePRO data collected is a quality of life questionnaire containing the WOMAC scale. The trial included more than 600 patients at 30 sites.

If the design of the study protocol and the PRO instrument

aims at being comparable across different devices, and the study population is chosen such that the subject's own device can be used for data collection, then clinicians can run one of the new breed of ePRO trials already out there.

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Alan Yeomans *is Quality Manager, Pharma Consulting Group, email: Alan.Yeomans@pharmaconsultinggroup.com.*

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How Mobile Technology is Evolving in Clinical Trials

Tim Davis

Analyzing the emergence of mobile customization in meeting the specific requirements of studies.

It is estimated that mobile penetration now stands at 96% globally, with significant growth in subscriptions in the developing world in recent years, increasing from 69% of the population in 2011 to 89% in 2013.[1,2] As access to devices expands across the globe, the use of mobile technology in all walks of life has become commonplace. As a result, mobile communication has been leveraged to provide information and access to services across multiple industries, from simple applications such as checking train timetables to mobile banking with secure access to personal information in a highly regulated industry. Clinical research is no exception to this trend and, indeed, the drug industry has seen an increasing movement to leverage mobile technology to engage with patients and collect their data during clinical trials.

The evolution of mobile in clinical research

In many ways, the inclusion of mobile phones and other devices in the clinical arena has been an evolution. The first step began almost a decade ago with the use of short message service (SMS) messages to address the retention and compliance issues so commonly faced during research. The scale of the problem was accurately brought home in a recent article in the Drug Information Association's (DIA) journal, *Therapeutic Innovation & Regulatory Science*, which revealed that as many as 30% of clinical trial participants do not take their study medication correctly.[3] The main reasons cited for non-adherence include forgetfulness;[4] poor communication with healthcare professionals,[5] especially in remote locations; and absence of symptoms.[6] An additional challenge is to retain subjects for the duration of the trial and reduce the number of patients lost to follow-up. In its recent "Perceptions and Insights Study," the Center for Information and Study on Clinical Research Participation (CISCRP) found that patients who drop out of clinical studies tend to be less self-motivated, less confident, and less understanding of the process.[7]

Mobile technology provided a means for researchers to communicate with patients remotely between site visits through a medium that patients carried with them wherever they were. It provided an effective system for sending reminders to ensure timely actions such as clinic visit attendance, fasting, correct drug intake, etc., while also establishing the means to communicate much more broadly with the patient, serving as a two-way open communication channel that allowed patients to respond to prompts as appropriate. This was the first step toward mobile electronic patient-reported outcome (ePRO) collection.

The introduction of these "retention and compliance" services enabled sponsors to monitor safety, manage compliance, and ensure patient retention throughout the study. For example, in a cardiovascular outcome event monitoring trial, a mobile communication service was included to help maintain contact with patients between subject visits, with a view to increasing the likelihood of the patient reporting if and when an event occurred. The use of this mobile service resulted in a 5% increase in visit compliance and a 4.5% reduction in early patient withdrawal compared to those not using the service. Moreover, in a study of 13,000 patients, it was estimated that if used across the entire study, this would have equated to a four-month earlier finish, resulting in the pharmaceutical sponsor saving more than $14 million in costs.[8]

The rise of mobile ePRO solutions

The rise of mobile ePRO tools has transformed the way patients engage in clinical trials. The ability to provide familiar technology to patient populations facilitates the collection of time-stamped data, and as mobile technology has propagated across the globe, it serves as an ideal mechanism for communicating and collecting data from hard-to-reach patients in developing markets such as Eastern Europe, Asia Pacific, and Latin America.

With patient compliance rates typically as low as 55%,[9] it is important to ensure the simplicity of the data collection interface. ePRO solutions can provide a simple, familiar, and effective modality to communicate and collect data and information from patients. As users are already familiar with the technology, they can navigate familiarly through the different steps of the data-collection process. As a result, these tools facilitate simple, real-time, and reliable collection of data from study participants, regardless of age or demographic.

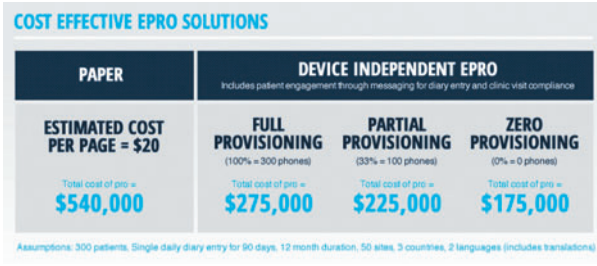
Mobile ePRO solutions can be customized to suit the specific requirements of each trial. The assessment could be a series of text messages sent intermittently to a patient's mobile phone to deliver online questionnaires, which can then be answered instantly via the mobile device. Alternatively, assessments can be delivered via an app—a route which is particularly useful when patients are in regions likely to have limited connectivity; data can be stored within the app and transmitted when connection is available. The use of an app also enables automated connection to medical devices such as blood glucose meters and spirometers via Bluetooth connections.

Mobile also allows for the inclusion of validated instruments in PRO. To achieve this, the author must approve the use of the scale in question; this is typically achieved through a usability study to ensure patients can interact with the electronic version and a validation study to assess equivalence compared to existing modes of delivery. An example of such a study is the m-WOMAC Osteoarthritis Index, which was found to be valid and reliable using a simple mobile phone Internet connection, showing no difference between mobile and paper scores.[10]

Introducing BYOD into clinical research

The traditional model for collecting ePRO measures has been to provision devices, seeking the assurance of fixed parameters for data viewing and validation. Until recently, this option has been fairly restrictive, providing a single device to all populations across each trial, regardless of their familiarity with the technology. However, advances in technology have enabled the onset of a "bring your own device" (BYOD) approach through the ability to recognize device parameters and optimize the configuration of data according to the device in use (e.g., laptop, tablet, mobile phone). The growth of digital and mobile technology means that many patients already own a device that can be used during the study. Device analysis can easily be integrated into patient enrollment and device provisioning can typically be reduced to as little as 10% or 20% of study participants. In some cases, this approach will remove the need for provisioning altogether such that the patients' own devices are employed throughout the study.

Cost Savings



Source: Davis

Figure 1. Cost comparisons between paper and electronic-based reporting tools.

A BYOD approach delivers a cost-effective strategy to engage patients through sharing information and capturing data on their own devices. The requirement to provide devices is reduced, or even removed altogether, as is the logistical challenge of managing large quantities of devices across the globe. An illustration of the cost savings that can be achieved is shown in Figure 1.

The first step toward BYOD was taken in late phase trials, where collecting real-world evidence from diverse populations is often especially challenging. Unlike the small populations that are closely managed by clinical trial sites in pre-approval clinical research, late phase studies require management of large, diverse populations by physicians and healthcare professionals (HCPs) over long periods of time with fewer "touchpoints." As a result, providing patients with hardware for electronic data capture (EDC) has historically been cost-prohibitive, so trials began to include online self-reporting as an alternative to paper data capture.[11] It is now possible to extend this BYOD opportunity through platforms designed to capture data securely from any connected device. Through recognizing the device being used and optimizing the content accordingly, identifying personally identifiable information (PII), and having internal procedures in place to secure this PII, a BYOD approach can be used with confidence as part of an efficient clinical strategy.

While there are existing examples of pre-approval BYOD use, such as the vaccine trial case study highlighted on the next page, the final stage in the evolution of mobile in clinical trials will be the broad use of a BYOD approach in Phase II and III trials. This is currently a hot discussion topic across the industry.[12,13,14,15] Existing evidence supports scale equivalence across multiple modalities, such as the PROMIS study using interactive voice response (IVR), paper, personal digital assistant, and computer,[16] and the ability to identify exact specifications of devices in use (screen size, operating system) and to block their usage if they fall outside of the validation range.

Reshaping the industry

Assessing the current landscape of the pharmaceutical industry, it is evident that mobile technology has a large role to play in improving the quality, simplicity, and ease of use of ePRO across the clinical-to-real-world continuum. The opportunities mobile solutions hold for the industry are vast, with the potential to reduce the major financial burdens as a result of increasing pressure to accelerate the path of drug candidates through clinical trials. In late-phase and real-world studies, especially, where adherence is often a major issue, mobile solutions provide an opportunity to incorporate patient engagement features to increase adherence and, as a result, collect more accurate, unbiased data.

Mobile technology is increasingly being implemented as a means of communicating directly with patients across broad demographics and multiple locations in both clinical studies and healthcare programs. The familiarity and universal nature of mobile devices and the ability to select the right tool according to the type of study that is being conducted, region, and demographic, makes the technology well-placed for integration into global markets.

Case study—BYOD in a vaccine surveillance study

Study overview: A Phase III, observer-blind, randomized, multicountry, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of an influenza candidate vaccine administered intramuscularly in 3,150 healthy children six months to 35 months of age across multiple countries in Europe.

The primary endpoint for the study was the efficacy of vaccine in the prevention of RT-PCR confirmed influenza A and/or B disease for any seasonal influenza strain, when compared to non-influenza control vaccines.

Data capture solution: The use of a BYOD approach offered parents the flexibility to use their preferred means of contact for completing diary entries. Eighty-four percent of parents/guardians opted to use their own mobile phone or personal computer, thus vastly reducing provisioning requirements for the study.

Results: The use of EDC provided greater resource efficiency and timelier follow-ups for the research team, as the switch from weekly to daily contact was symptom-driven, and, therefore, management would have been immensely complicated and resource-intensive using paper.

Given the study's scale and geographic spread, 100% provisioning would have been cost-prohibitive, both in terms of purchase of devices, as well as the associated logistics, maintenance, and support necessary. With 84% of parents/guardians using their own device, the BYOD enabled a data capture method that previously was not possible. Parents/guardians benefitted from a user-friendly interface (with automated decision-making via branching logic in the eDiary) and being able to contribute from the familiarity of their own device (minimizing end-user training). They were able to complete assessments and report outcomes throughout the trial in the simplest possible way. This empowered parents/guardians to steer their participation and ultimately improve their child's health. It also enabled high levels of data entry compliance. Considering that the average provisioning cost per device (including setup, monthly data charge, and monthly lease) was $400, the savings were clear to see—and were expected to total almost $3 million upon study completion.

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Tim Davis *is CEO and Co-founder of Exco InTouch; email: tim.davis@excointouch.com.*

Steps for a Successful Clinical Trial Management System

Erika Stevens, Christina Eberthart, Jim Moran

Academic health centers are assessing options to better control the flow of data and boost compliance.

As the importance of translational research continues to grow, with focus placed on comparative effectiveness and outcomes-based research through translational science awards[1] and the American Recovery and Investment Act,[2] research institutions are exploring other options to remain competitive players in the academic clinical research arena. Among the options, many academic institutions are partnering with the federal government and industry to reinvest in bench research and clinical trials.[3,4] The results of this investment have been an increase in the number of clinical research trials being conducted simultaneously, as well as a rise in the number of investigational products (including devices and biologics) being tested. This combined effort has placed a compliance burden at academic research institutes (AMIs) or academic health centers.[5] To mitigate compliance issues and gain operational efficiencies, many academic centers are implementing clinical research software solutions to assist in managing the flow of information in their growing clinical research portfolios.

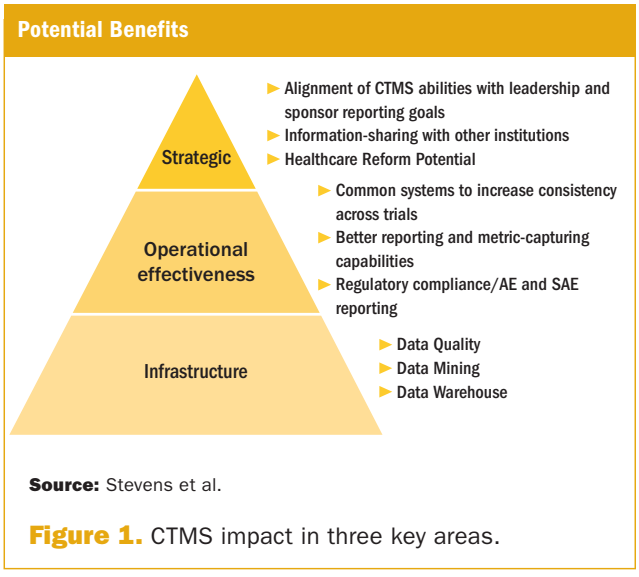
Exploring the benefits of clinical trial management system

As mentioned above, academic research institutions are assessing options to better control the flow of information and mitigate compliance issues in non-clinical and clinical research trials. One option for academic institutions is to implement a fully integrated clinical trial management system (CTMS). CTMSs are designed to be customizable enterprise-wide solution to manage, collect, and analyze data collected during the entire preclinical and clinical trial process. The benefits of mapping and developing an enterprise wide solution include:[6]

- Centralizing decentralized departments
- Optimizing institutional review board (IRB) functionality
- Realizing real-time data available to both investigators and leadership
- Decreasing bottlenecks in knowledge transfer between various entities involved in research
- Reducing human errors in reporting that often cause compliance issues
- Tracking milestones for grants, awards, fellowships, etc.
- Streamlining the financial structure—billing and invoicing

By implementing a CTMS, AMIs are moving away from antiquated non-integrated manual processes and turning to technical solutions to manage the flow of information associated with conducting clinical trials.

A successful CTMS can provide a well-organized flow of knowledge throughout the institution and assist senior management in obtaining real-time data to better analyze the current state of their clinical research enterprise. Armed with milestone-based, real-time data, senior management, such as business unit directors and department chairpersons, are better equipped to make strategic decisions to improve overall operational effectiveness, compliance, governance, and infrastructure (see Figure 1 on page 24). The following list highlights some of the operational, infrastructure, compliance, and governance issues that can be improved through the implementation of a CTMS:



Source: Stevens et al.

Figure 1. CTMS impact in three key areas.

- **Staffing**: With a better understanding of resources, management will be capable of reallocating staffing assignments to offset excess or inadequate roles.
- **Communication:** Improved communication will improve patient satisfaction and monitoring of clinical trials.
- **Human error:** CTMSs have integrated checking components to limit errors in reporting.
- **Operational flow:** Improved knowledge flow in various divisions (finance, marketing, administration, training, and recruitment) will help to achieve real-time results and data.
- **Managing clinical data:** More accurate and efficient reporting tools will be useful internally and externally for current and future project assessments.

Choosing a CTMS that serves your institutional needs

There are three general types of CTMS: web-based, cloud-based, and on-site hosted-based software.[7] Each type has distinct advantages and may have disadvantages depending on the IT infrastructure at the respective academic medical center. In order to understand your institutional needs, we suggest starting with defining the purpose or mission of your CTMS. Once the mission(s) or purpose is defined, then the disparate systems or system gaps can be assessed and mapped. During the mapping exercise, consider exploring the following missions and/or purposes to build use cases of a well-balanced, operationally efficient, and compliant CTMS:

- Improvements in clinical, administration, and financial management of research
- Fostering and improving collaborations among investigators
- Greater understanding of the progress and revenue impact of clinical trials
- Increasing subject recruitment and safety through the institution
- Reducing errors and increasing facility compliance
- Operating efficiently and saving research time

Prior to purchasing or implementing a CTMS, it is necessary to assess the institution's operational, compliance, and governance needs and priorities, as well as outline current software systems (see Table 1 on facing page). Establishing priorities and identifying current systems can be done in mapping sessions. In these sessions, a cross-functional team of principal investigators, study coordinators, and senior leadership (such as the chief information officer, chief financial officer, human resources representatives, and chief compliance officer) are allowed to identify future system requirements, outline current software system gaps, and weigh operational, governance, and compliance priorities. For instance, leadership may insist upon certain compliance management reporting capabilities, while investigators may require that the system track pre-award study start-up milestones, financial reconciliation, and integrate with electronic health records (EHR). Next, a gap analysis of the research institute's current software system's capabilities and the requirements identified in the mapping sessions versus CTMS-specific capabilities is completed. The will help to identify the best CTMS fit for the institution.

After this step, the vendor selection process can begin. Based on the mapping, most institutions will not be able to pick a system off the shelf that is fully operational for their clinical research needs. This makes choosing a system somewhat more complicated than implementing many other types of institutional systems, such as financial, electronic health management, and other point of service systems. CTMSs have the potential to solve many of the compliance, governance, operational, and managerial issues at academic medical centers with analytics and reports. So which system do you choose? Unfortunately, for these institutions, currently there are no perfect, one-size-fits-all CTMSs available in the market. Even though there is no perfect system, consider reviewing of some common elements among most of the best systems:

- Financial reporting tools (coverage analysis, residual and overage reporting)
- Clinical trial management tools (including applicable clinical trial milestones and reporting dashboards)
- Searchable clinical trial database
- Analytical risk-based decisions
- Reporting dashboards
- Data warehousing module
- Recruitment support module
- Electronic case report form (eCRF)
- Integrates easily with electronic medical records (EMRs), institutional review board (IRB) system(s), etc.

As the market demand for computerized CTMSs increases, so does the number of systems solutions. Thus, we may be getting closer to a system that effectively manages all aspects of the clinical trial process at academic centers. Until then, any CTMS implementation will require a certain amount of mapping, customization, and implementation support, and may not serve all analytical and reporting needs.

System Selection		
Internal socialization and planning	•	Define mission/purpose Seek key stakeholder feedback/approval Develop an internal/institutional budget, etc.
Requirements gathering	•	Gather user and reporting requirements (enterprisewide use case(s)
Development of a request for proposal (RFP)	•	Nominate a Steering Committee Develop an RFP based on requirements Outline the details of what information is required and requested relating to implementation timeline and costs for configuration, integration and interfaces
System demos	•	Perform demos with vendors of select RFP responses after selection has been narrowed
RFP review and decision	•	Steering Committee to review RFPs, participate in system demos, and select a vendor that most closely aligns with requirements and price

Source: Stevens et al.

Table 1. Important considerations when choosing a CTMS.

Cost factors and implementation overview

CTMSs can come with a hefty price tag. In our experience, the purchase and implementation of a CTMS often means a commitment of two or more years and costs can run into the millions of dollars. It is essential to take all implementation costs into consideration before choosing a CTMS. Many systems offer somewhat low "off the shelf" prices, but these prices don't reflect the true cost. It is necessary to consider not only the cost of the system itself, but the cost of customization, migration of data from legacy systems (EDC and data warehouses), integration with other disparate research (IRB, Lawson, EHR) systems, training, and roll-out timeline when choosing a CTMS. One other cost consideration is to engage a third party to assist during the system selection and implementation phases to provide program management for such a large investment.

In our experience with the implementation of CTMSs, the following are key aspects of the process:

- **Building a steering committee:** The most important aspect of implementing a CTMS is having a committee that is capable of making well-informed decisions for the institution.
- **Forecasting future issues:** Know the current and future issues of the institution that hope to be resolved with the CTMS.
- **Adapting to change:** Understand that implementing a CTMS will come with new responsibilities. The institution should be prepared to have individuals fill these new roles. Without this preparation, the CTMS is doomed from the beginning. New hires might not be necessary, but rather a shift in responsibilities. Create a culture of transparency to eliminate conflict and inconsistencies in the future.
- **Training and preparation:** Design an ongoing tailored training program to meet the short- and long-term needs of staff. Implement training and train staff on the new technology.
- **Hiring an external firm:** Consider bringing in an unbiased firm to help people in the institution understand the true benefits of change. Theå firm can also provide management with options for implementation, interface, and utilization.

Conclusion

In today's clinical research environment, it is no longer enough to have a disparate stand-alone system that tracks clinical trials. In reality, a successful CTMS solution will require integration with other systems such as EHR, IRB, and financials linking all preclinical and clinical research processes together. This integration creates a powerful database for clinical trials management, enabling AMIs access to real-time data and allowing them to maintain and manage various stages of clinical trials through CTMS data analytics.

Along with strategic, governance, and operational improvements, a successful CTMS can improve patient satisfaction, increase return on investments, enhance communication between departments, increase the volume of completed trials, and generate an overall more efficient clinical research portfolio.

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Erika Stevens *is Senior Manager*; **Christina Eberhart** *is Manager*; *and* **Jim Moran** *is Executive Director, all in the Advisory Services practice of Ernst & Young.*

Note: *The views expressed are those of the authors and do not necessarily reflect the views of Ernst & Young LLP.*

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Please contact the *Applied Clinical Trials* staff with your questions and comments. We look forward to hearing from you.

We hope this resource will be a valuable one.

Best Regards and Cheers,

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TELEPHONE
+39-045-8222811

FAX
+39-045-8222812

North America Headquarters
One Alewife Center,
Suite 120
Cambridge, MA 02140

TELEPHONE
617-871-1128

FAX
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New challenges, new opportunities

DIA has always played a vital role in maintaining the skills and network of health product development professionals. That need is more pressing than ever. New understanding of disease processes, new regulatory approaches, and the increasing influence of information technology is accelerating and diversifying healthcare innovation.

How professionals react to this challenge will be vital. Embracing this opportunity will build upon Europe's status as a hub for healthcare innovation, stimulating further investment. However, all stakeholders have a role to play in creating an environment where research and regulation are mutually supportive. This means providing effective platforms for discussion and knowledge transfer.

DIA, with more than 18,000 members, is the perfect organisation to provide these platforms. It has an enviable track record in bringing together innovators, regulators and influencers. This is why the DIA EuroMeeting 2015 is the ideal opportunity to equip all businesses with the knowledge and network to prepare for these challenges future, wherever they sit in the value chain. The meeting is based around 12 highly topical, relevant themes. Headline topics include the new clinical trial legislation, regulatory coordination and the impact of big data on healthcare.

Creating a Global Healthcare Village

However, DIA Meetings offer more than listening and learning; they are a community. The EuroMeeting provides a unique microcosm of the health product development environment; three days of high-quality networking and knowledge exchange. The 2015 EuroMeeting brings further refinements. By combining the DIA EuroMeeting and the Clinical Forum Exhibition into a single site, it will turn the Palais de Congrès in Paris into a Global Healthcare Village. With more than 2,500 stakeholders in one place, no other conference offers such a comprehensive array of stakeholders and fellow experts spanning the entire healthcare value chain.

DIA DEVELOP INNOVATE ADVANCE

Join the conversation: #DIAEuro LinkedIn DIA (DrugInfoAssn)

27th DIA Annual EuroMeeting

13-15 April 2015 | Palais des Congrès | Paris

Development, Innovation, Access and Patient Safety

Healthcare innovation is accelerating and diversifying to meet the demands posed by societal change. The impact on your business environment is equally dramatic. The shift to patient-centric business models is already revolutionising how we do business in Europe

- How can you keep your professional knowledge up to speed?
- How do you ensure that your network is up to date?
- How will you identify and meet the right partners in your company's innovation value chain?

Find the answers to these challenges – and many more - at the DIA EuroMeeting 2015.

The DIA EuroMeeting 2015 offers you a microcosm of the evolving European healthcare landscape, built around three days of high-quality networking, partnering and knowledge transfer opportunities.

- 12 highly relevant, thought-leading themes
- Contacts, networking and solutions - all on a single site
- New for 2015: DIA EuroMeeting and the Clinical Forum Exhibition in a single venue.
- More than 2,500 health product development professionals at a single venue

Meet the individuals who can provide the answers to your challenges: Professionals in the pharmaceutical and biotech industries, CROs, clinical trial sites, health regulatory agencies and delegates from academia and patient organisations and many more.

Visit www.diahome.org/EM2015 for more information

DIA DEVELOP INNOVATE ADVANCE

DIA Europe, Middle East and Africa
Kuechengasse 16
4051 Basel, Switzerland

ERT

Corporate Description
ERT is a leading provider of high-quality patient safety and efficacy endpoint data collection solutions for use in clinical drug development. By integrating innovative solutions built upon a scientific and regulatory foundation, ERT collects, analyzes, and delivers reliable safety and efficacy data critical to the approval, labeling, and reimbursement of pharmaceutical products, while improving clinical development efficiency. ERT is the acknowledged industry leader in:

Multi-Mode eCOA Solutions
When it comes to capturing electronic Clinical Outcome Assessment (eCOA) data (which includes PROs, ClinROs, and ObsROs), only ERT offers all proven modalities: mobile handhelds, tablets, IVRS, and web. ERT's technology, scientific, and regulatory experts can be relied upon to help sponsors determine the most effective modality and approach for collecting eCOA data—whether through dedicated devices, Bring Your Own Device (BYOD: available on mobile apps, web, and IVRS) or a hybrid solution of both approaches. By working with ERT, sponsors eliminate patient compliance issues, avoid inaccurate, incomplete, or illegible data, and ultimately produce better-informed data.

Suicide Risk Assessment
ERT's proven electronic suicide risk assessment system, AVERT™, enables biopharmaceutical companies to comply with regulatory requirements for prospective monitoring of suicidal ideation and behaviors (SIB) during clinical development. ERT's exclusive electronic self-rated version of the Columbia Suicide Severity Rating Scale (eC-SSRS) is a cost-effective and reliable method of prospectively monitoring for SIB, and is specified as an appropriate means for capturing this important data in the FDA's revised Draft Guidance.

Scientific and Regulatory Consulting
ERT's consulting group harnesses the industry-leading expertise of its cardiac safety, respiratory, and COA scientists to support the clinical development needs of biopharmaceutical researchers. ERT's consulting group offers reliable services that support the regulatory approval and commercial optimization for new medical treatments in development.

Centralized Cardiac Safety
ERT's Centralized Cardiac Safety solution utilizes newly developed software technology, within its best in class EXPERT® operating platform. The technology enables the collection of real-time, consistent, and high quality information, easing site operations and delivering better value to biopharmaceutical companies. Significant cost savings can be recognized as a result of the improved data quality and processes associated with the use of centralized cardiac safety.

Respiratory Solutions
ERT is the industry leader in Centralized Spirometry and Pulmonary Function Testing. From device customization to clinical data analysis, ERT provides products and services that ensure the most accurate data and efficient trial management in the industry. ERT's respiratory services, now fully in the EXPERT® operating platform, offer quality control, real-time views of data through a user-friendly web portal, and Best Test reviews of unacceptable data.

Universal Data Integration, Analytics, and Visualization
ERT's innovative cloud-based software platform—eClinical Insights—enables trial sponsors to integrate data from multiple systems and gain full visibility across the key aspects of their trials. This proven, cloud-based software simplifies data collection, analytics, visibility, and exchange. The end result is comprehensive insight into investigative site and outcomes data activity, true risk-based management, enhanced performance measurement, and informed real-time decision-making through a single interface.

For more information about ERT's leading solutions, visit: www.ert.com

ERT
1818 Market Street
Suite 1000
Philadelphia, PA 19103-3638

TELEPHONE
215-972-0420

FAX
215-972-0414

E-MAIL
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Eurofins Central Laboratory

About Eurofins Central Laboratory

Reliable, high-quality laboratory data is pivotal to the success of clinical trials. Since laboratory testing is our sole focus, we go above and beyond to provide an array of services to ensure that any clinical trial sample is collected, transported, managed, analyzed, reported, and stored to meet the objectives and purpose of your study. We are dedicated to providing the most cost-effective and efficient solutions to pharmaceutical and biotech companies, and CROs alike.

Eurofins Central Laboratory is uniquely positioned with its Clinical Biomarker Services by uniting GLP and GCP in one synergetic approach. This hybrid system allows us to combine the best of two worlds when utilizing laboratory biomarkers to prove safety and efficacy, support go/no-go decisions, patient stratification, and submission of data sets to regulatory agencies. Supported by a strong and experienced Scientific Affairs Committee, biomarker assays are development and validated fit-for-purpose to meet the specific requirements of the Clinical Trial Program. Using our scientific expertise, biomarker assay are evaluated for their feasibility when progressing these assays to a testing production environment.

Eurofins Central Laboratory supports its customers with 5 wholly-owned CAP accredited laboratory facilities in the United States, Europe, India, Singapore, and China. Our harmonized laboratories operate as one. All of our laboratories are connected to one global LIMS and are using the same global standard operating procedures and global reference ranges through the deployment of uniform instruments, reagents, and analytical methods to provide one global data set for submission to health authorities worldwide.

Laboratory Testing Capabilities

Global clinical safety and specialized testing—Full package of routine and non-routine laboratory testing, including:

- Hematology
- Immunochemistry
- Urinalysis
- Coagulation testing
- Flow cytometry
- Biomarkers
- Hormones
- Cell markers
- Cytokine profiling
- Infectious disease serology
- DNA/RNA isolation and long term storage
- Routine genomic testing

Biomarker Services

- Fit-for-purpose advanced validation and analysis of commercially available biomarker assays
- PK analysis of endogenous compounds (large molecules)
- Feasibility assessment and scientific consultancy

Global Infectious Disease Services

- Central laboratory microbiology to support clinical trials
- Clinical virology services
- Scientific consultancy

Clinical Trial Supporting Services

- Logistics support and courier management
- Import and export licenses consultancy for Asia-Pacific
- Investigator site support
- Multilingual regional helpdesk on three continents
- Sample management and storage
- Project management
- Data management

IT Systems and EDPs

- Real-time validated global results database via secured Eurofins Data Portal (EDP)
- Flagging alerts for out-of-range test results
- Trend analysis tools
- Study-specific, customized analysis tools upon request

Global QC and QA

- Global lot # for controls and calibrators for global instrument calibration
- External proficiency testing programs (e.g., CAP, EQAS, NEQAS, Randox, NGSP Level 1, CLIA, ISO 151089, ISO 17025)
- Bi-weekly internal proficiency testing for all Eurofins facilities and standardized partners

Eurofins Central Laboratory
Headquarters:
2430 New Holland Pike
Lancaster, PA 17601
Tel +1-717-556-7350
Fax +1-717-556-3888

Breda, The Netherlands
Tel +31-76-572-7272
Fax +31-76-573-7778

Singapore
Tel +65-6562-3858
Fax +65-6562-3086

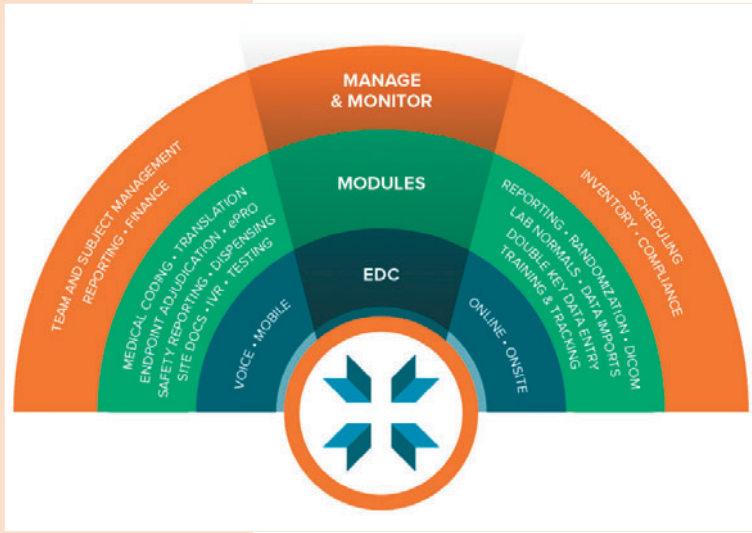
Shanghai
Tel +86-21-6181-7500
Fax +86 21-6181-7501

E-MAIL
clinicaltrials@eurofins.com

WEBSITE
eurofinscentrallaboratory.com

NUMBER OF EMPLOYEES
250

Merge eClinical



Corporate Description

Merge eClinical develops and markets smart software that streamlines the clinical research process. Our company is built on the belief that every study—no matter its size, location, or research setting—deserves the benefits offered by information technology to improve safety, quality, and study outcomes. eClinicalOS™ (eCOS) is a single, scalable cloud-based platform that lets clinical research professionals design, launch, and manage trials with more control, convenience, and confidence than ever before.

The eCOS platform was formally introduced in 2012. Since then it has become the fastest-growing software platform in the sector. Merge eClinical is a division of Merge Healthcare, Inc. (NASDAQ: MRGE), a leading provider of clinical systems and innovations that seek to transform healthcare.

Major Products/Markets Served

With headquarters in Research Triangle Park, N.C., and offices around the globe, Merge eClinical serves researchers in all industry categories: pharmaceutical and device manufacturers, CROs, and academic institutions. Through active sites in 80-plus countries, more than 50,000 clinical research professionals in small and large organizations have entrusted their data and study management needs to our flagship product, eCOS. With a unique pay-as-you-go model, you choose only the features you actually need; eCOS allows you to scale up or down to suit a study's precise requirements. No upfront licensing fees are required, and focused training allows you to manage studies independently.

With eCOS, you have the freedom to configure a solution that meets your team's evolving needs.

Some of the highlights coming in 2015:

Through our "We Support You" program, customers can access new and improved online training manuals and videos. As always, expert eCOS-certified designers are available anytime to help with study design, real-time troubleshooting, or just about any question or need you may have. Users will also have opportunities throughout the year to meet with us for roundtables, forums, and on-site training events. Customers can also expect to see innovations in our risk-based management and an evolution to our clinical trial management system.

Merge eClinical
4000 Aerial Center
Parkway, Suite 101
Morrisville, NC 27560

TELEPHONE
919-653-3400

FAX
919-653-3620

E-MAIL
info@eclinicalos.com

WEBSITES
www.merge.com
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Spectra Clinical Research

Nicholas Brownlee, PhD, President

We pride ourselves in working side-by-side with our customers to understand their specific needs and move their trial toward success.

Corporate Description

Spectra Clinical Research provides central laboratory services to pharmaceutical companies, academic institutions, and other medical organizations conducting Phase I–IV clinical trials. Backed by over a decade of clinical trial expertise and 30 years of central laboratory services to the dialysis community, we are able to support diverse clinical trials of all sizes.

Spectra Clinical Research acts as a unique resource for organizations conducting clinical trials. As a division of Spectra Laboratories, we leverage the capacity and technology of a large organization while maintaining the flexibility and responsiveness of a small specialty laboratory. We continually review and streamline our processes to ensure timely, accurate results. Furthermore, our advanced testing platforms, specimen management, online data management application, and dedicated team of service specialists help move each trial toward a successful outcome.

Markets Served

Spectra Clinical Research provides central laboratory services to pharmaceutical, biotechnology, research, government, and academic organizations. We have participated in trials spanning a wide range of therapeutic areas including nephrology, gastroenterology, oncology, women's health, and central nervous system (CNS) disorders. Our global support network ensures continuous, reliable service for clinical trials in locations worldwide including North America, Israel, South America, Europe, Australia, South Africa, Asia, and India.

Products and Services

- A dedicated project manager prepares all study-specific documents, coordinates activities with partner laboratories, and attends investigator meetings.
- Specially trained personnel shepherd each sample through the laboratory.
- Designated customer service representatives assigned to each study ensure personalized assistance throughout the trial.
- Support for numerous esoteric tests includes soluble transferrin receptor, aluminum, zinc, I-PTH, and others.
- Microbiology department offers 24/7 testing services for bacteriology.
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Spectra Clinical Research
8 King Road
Rockleigh, NJ 07647

TELEPHONE
201-767-2349
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Clinical Document Exchange Portals: Trendy or Revolutionary?

While the discussion around pain points in developing pharmaceuticals isn't new, we are only now starting to see solutions emerge.

Kevin Wojcikewych
Senior Director, Business Optimization, Novella Clinical
E-mail: kwojcikewych@novellaclinical.com

Clinical trial inefficiencies have been well documented and are commonly cited as one of the main drivers of the escalating cost of drug development. So while the discussion around pain points in developing drugs isn't new, we are only now starting to see solutions emerge. The most recent significant development came from the non-profit TransCelerate, which plans to unveil a shared investigator portal accompanied by an outline for new technology standards that foster interoperability.

Portal innovation is also coming from vendors which offer portal products with a variety of functionality. Even some contract research organizations (CROs) have launched portal products—recognizing the inherent benefits of reduced study start-up time and more efficient processes for themselves and their customers.

The question then becomes, what do the trial sites want? According to a 2013 site survey by CenterWatch and Intralinks, 80% of respondents said they would find value in a single-login trial web portal that allowed access to multiple sponsors. In 2011, a similar survey conducted by the same parties found that 73% of sites were still using traditional communication methods—email, fax, and courier—as their primary tool for exchanging clinical trial documents.

With study inefficiencies still present, and sponsors, vendors, CROs, and sites presumably on board, the industry is still quite early in the adoption of investigator portals despite the promise they hold. The following are some of the most impactful benefits investigator portals can provide to both sponsors and CROs.

Online Site Profile & Registration

Sites and site staff, through a single sign-on, enter required information and upload key documents just one time during study initiation. This information is then used to prepopulate documents downstream, and can be used for future and ongoing studies. Only a small validation step would be needed to ensure the information is current. Benefit: Reduced cycle time during site start up.

Secure Document Exchange with eTMF

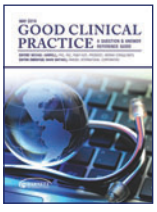
Manually tracking the status of required site documents wastes a considerable amount of time. It can be days before a CRO or sponsor realizes a document is missing. Additional time is then needed to collect the forgotten document. With a secure document exchange, sites are proactively notified of missing information. This "trigger" can also dramatically reduce the time needed to get a site qualified and activated. Benefit: an estimated 20% reduction in document collection/maintenance costs.

In addition, all documents can be stored and accessed through the electronic trial master file (eTMF), as opposed to having hard copy files at the site. This cloud-enabled "virtual document binder" would serve as the single source of site documents, reducing the need for clinical research associates (CRAs) to reconcile site files to the eTMF during a site visit. Benefit: an estimated 10% reduction of on-site CRA time.

Integrated Learning Management System

As the industry becomes more willing to standardize training across sponsors and CROs, an integrated learning management system (LMS) not only reduces the administrative time needed to track where sites are within the compliance process, but also in potentially limiting the need for duplicative site trainings. Additionally, an integrated LMS could eliminate training duplications from previous studies by automatically tracking who has received certain training. Benefit: reduce CRO or sponsor efforts and costs of training administration and compliance by an estimated 25%.

Essential Publications for **Clinical Research Professionals**



Good Clinical Practice: A Question & Answer Reference Guide

This industry-leading guide answers over 1,200 of the most common and difficult questions regarding the interpretation and implementation of US and International GCP standards.

Barnett's Self-Instructional CRA Training Series

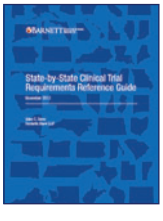
Focused on the day-to-day work of the monitor, this 7-volume self-study series provides the basics of CRA requirements in today's environment.

Barnett's Self-Instructional Study Site Training Series

Providing the essential tasks, roles and responsibilities of the clinical study team, this 6-volume series covers study site requirements through self-paced learning activities.

HIPAA & US Clinical Trials

Designed for organizations that sponsor, conduct or oversee clinical trials in the US that depend on usage and disclosure of research subjects' health information.



State-by-State Clinical Trials Requirements Reference Guide

Covering clinical trial standards in all 50 US states, this resource breaks down each state's requirements in more than a dozen practical areas.

- CFR/ICH GCP Reference Guide
- CFR/ICH GCP Reference Guide for Medical Devices
- Glossary & Acronyms for Clinical Research Professionals

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