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PATIENT AS THE SOURCE

ENABLING TECHNOLOGY FOR PATIENT-CENTERED CLINICAL TRIALS

CRAIG LIPSET, Director of Clinical Research at Pfizer, leads a panel discussion on the current state of clinical trials and the use of technology to capture the voice of the patient. The panelists, coming from various backgrounds, lend their differing viewpoints on the current and future trends in this space

CRAIG LIPSET What are some of the touch-points for engaging patients in clinical trials and how are we engaging patients today?

TIM DAVIS It isn't all doom and gloom. Speaking from our own experience and from our customer feedback, one of the clearest touch points in the world today is the mobile or cell phone channel. Over 4 billion people or two-thirds of the world's population already own a cell phone and that is three times the number of people who have access to the Internet (either at home, work or in an Internet cafe) or who own a tethered landline telephone. Therefore, it is common sense that this is a platform for patient engagement and we've seen that this can be really effective in areas of patient recruitment, patient compliance, long-term retention and motivation using a similar modality, right through to actually using the cell phone as an electronic diary that patients carry around with them every day to collect data regarding their condition, symptoms etc. »

THE PEOPLE

Today's patients strive to be informed and engaged. We're witnessing the rise of the e-patient: 61 percent of adults look online for health information, 37 percent of adults are using health 2.0 resources such as user-generated content, blogs and podcasts, and 42 percent of adults believe they or someone they know have been helped following medical advice online, according to the Pew Research Center.

THE CHALLENGE

The challenges for pharmaceutical companies are well known. Pharmaceutical development cycles remain long and costly while success rates remain low (16 percent of drugs entering clinical trials receive approval). Over the last two decades, industry investments in R&D have increased while the number of new medicines introduced to the marketplace have fallen by about half. Additionally major patent expirations are looming and there is the influence of a rapidly changing external environment with many unknowns such as healthcare reform and reimbursement.

THE QUESTION

Patients are better informed and engaged. What does this mean for how we conduct clinical research?

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KARIN COYNE Patients today enjoy technology. They like to try out devices, they like feedback and they want to use an interface that is easy to use, which requires very little instruction in order to complete. They like the immediate feedback that can be provided with electronic technology. In terms of recruitment, we have been able to recruit online very rapidly. It greatly enhances how quickly we can recruit and enroll patients for our studies.

JOHN JORDAN At CRF Health we're involved with electronic patient reported outcomes and that is where I see most of the engagement with patients at this point in time. The electronic patient reported outcomes process with regards to providing hand-held PDAs to the subjects and allowing them to

enter data directly to the clinical trial database gives them a certain power and involvement that hasn't been seen in many years. In addition to the PDA handheld solution we provide, I agree with Tim that the mobile phone is becoming more of a touch point for the patient. With regards to the mobile phones there are functionalities available to send reminders or alarms to patients or SMS text messages as well to ensure the compliance and protocols are followed in the proper manner.

MIKE FEDERICO What we've seen when engaging patients is the necessity to use a simple but powerful solution that every subject is comfortable with and that they can then use throughout the patient experience. We've found that using the telephone, as Tim mentioned, is something that is very familiar to them and we're talking about just a regular telephone that has broad applicability. The success is in the simplicity of the 'low tech' solution. Major advantages of using this technique are that you avoid the illiteracy and comprehension problems, access difficulties and hardware issues.

Using something very familiar to your patients, the telephone, will get them involved in your clinical trials early and establish both buy-in and a direct line of access, which ensures that the patients will feel they're being looked after. As the study progresses, patients remain involved throughout the process, using the phone to perform assessments and screening, fill in electronic diary entries, and collect clinical assessments and safety monitoring data, until completion of your trial. Then as you move them into open label they're still using the same simple patient interface to do ongoing monitoring throughout a Phase IV trial. If we can simplify the interface with the patient; give them something they already know how to use, and have one modality throughout the patient experience, it is going to provide the most simple touch point and engage all patients throughout the trial and their ongoing care.

CL What are the various types of data we capture from the patient as source?

JJ The types of data that is captured in various clinical trials throughout the industry varies a great deal. In most cases when people hear the acronym ePRO (electronic Patient Reported Outcomes) most of the time what comes to mind is quality of life questionnaires, signs and symptoms, or compliance with taking medication at the prescribed time. In addition to the quality of life and additional questionnaires that are typically used in ePRO, we also have various dosing modules that are being utilized right now where pharmaceutical companies are requiring patients to take various medication at various times throughout the day, and ensuring that they are taken at the right times is critical to the success of their trials. So the scope of the data that is being collected is growing rather quickly within the industry. The expansion and adoption of ePRO is growing quickly as well. In addition to the data sources that I've spoken about, there will be many more to come in the years ahead.

MF Patient Reported Outcomes via, in this case, the telephone provide for a broad range of data we would like to collect — whether it's initial recruitment information or data collected during the trial. The PRO guidance defines PRO as taking information from the patient without it being processed by another human being. This is a great example of where PROs can be done electronically without that interface of someone sitting across from the patient conducting an interview or a clinical assessment and it then being processed through them and before finally being entered into the database. With the electronic PRO we can capture that data directly from the patient, whether it's a screening criteria, quality of life data or a clinical assessment.

The other aspects of the trial affected are around safety data and, in particular, suicidality monitoring is a hot topic for the regulatory agencies at the moment. As an industry, we want to be able to capture that this sort »



CRAIG LIPSET
DIRECTOR OF CLINICAL RESEARCH
PFIZER

Mr. Lipset brings over 15 years of leadership and innovation in clinical research. At Pfizer he leads initiatives in molecular medicine to advance personalized therapies, as well as in eHealth leveraging technologies to improve patient engagement in clinical research. He previously served as VP of Program Management at Adnexus Therapeutics (formerly Compound Therapeutics) with responsibility for clinical and regulatory affairs. Mr. Lipset was recently awarded the 2010 DIA Outstanding Service Award.



JOHN JORDAN
CHIEF OPERATING OFFICER
CRF HEALTH INC.

CRF Health Inc., is a leading ePRO software and services provider. Mr. Jordan is responsible for the Global Operations and leads the Client Services group within the organization. Prior to joining CRF Health, Mr. Jordan was the Global Head of EDC and ePRO and Assistant Director of Global Clinical Data Management at Schering-Plough Research Institute and was responsible for the Clinical Database Services (CDS) department. The CDS group managed and performed the development of the EDC portion of all studies conducted by SPRI.



MICHAEL FEDERICO
VICE PRESIDENT
EPRO SOLUTIONS, ERT

Mr. Federico is responsible for managing all aspects of the ePRO Solutions suite at ERT, including product development, operations, and sales. The ePRO group has organized ERT's capabilities into products and services to provide the complete patient experience from recruiting right through to suicidality monitoring. New products within the portfolio include new scales, diaries, Time-Line-Follow-Back, suicidality monitoring assessment and alerting services. ERT also offers established protocols for validating new ePRO services.

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of safety information directly from the patient without it being monitored or assessed by another human being. The fact that we're getting the information directly from the patient without additional processing or interpretation means we will be getting more accurate and credible data.

JACK MCKENZIE In the past, due to the limits in technology, physiological data was only collected in clinical settings. With the advancements that have been made in the technology of developing physiological measurements, we now can collect objective data in the patients' ambulatory environment. This decreases the noise-to-signal ratio so if you have an objective measurement, there is a better signal with less noise. In addition,

it reduces the patient burden. For example, the FDA was looking at the fatigue rating scale of a pharma study and decided they need an objective way to measure fatigue. In this case they used actigraphy to measure the activity of daily living, the number of naps, and the sleep the patient was getting. I think in order to measure the quality of life indicators that have been mentioned before, it is really important that we start to look at the physiological measurements and how those measurements align with some of the subjective measurements that are being collected.

CL What are some of the challenges to successful implementation of tools designed to capture the "voice" of the patient?

KC There are quite a few. Certainly how you ask a question alters the response of that question. How a question is presented, be it via phone, Web or PDA, will also affect the response, which is why user interface is so essential. There is a need to make sure that the instructions are clear and the answers are easy to select without, for instance, changes caused by the mouse without the patient knowing it. It is a blending of science and technology when we take a questionnaire or PRO from paper and place it onto any type of device or electronic interface.

Also, the final FDA guidance document highlights the point that you need to keep the format consistent with how it was originally developed. The wonderful thing about moving from a paper medium to electronic is that you can enhance the PRO and make it easier especially if there is a skip pattern involved. When going from a paper to an electronic modality if subtle things are changed, and typically they are especially with instructions and formatting, you need to verify that the intent or the meaning of the questions has not changed.

There are a few other challenges involved with this transition but they can be addressed with patient interviews and usability testing, which is critical when going from one format to the other.

JM One of the interesting things we in the industry need to address is the standardization of signals. For example, it is very easy to say a patient has a certain heart rate or respiratory rate, but when you get to other signals such as activity of daily living as recorded by accelerometers, or sleep, there needs to be standardization of those signals and of those reported outcomes to the FDA and to the regulatory bodies.

The other barrier that we're facing is the FDA's acceptance of physiological data. The best example is in the field of sleep. Right now the gold standard is polysomnography for insomnia, but polysomnography is not being reimbursed for insomnia whereas actigraphy is. We need to educate the FDA on the end points and how to move those end points forward. I think the other primary end point that we need to think about in measuring physiological is how to best get those to the patient with the least amount of invasion into their ambulatory structure.

TD We've seen the ePRO guidance which is very much how we expected it to be, there weren't any tremendous road blocks for any of the vendors involved in this phase. With regards to that regulation and also 21 CFR Part 11 I think now the majority of vendors can really show the validation credibility and regulatory rigor demanded by sponsors. The majority of responsible organizations are comfortable with the approach and the delivery taken.

With regards to HIPAA and HIPAA equivalents around the world, we are quite fortunate in a sense that we are working in 60 countries and have a good insight into that. HIPAA itself is fairly easy to manage within the clinical trials framework because it is handled and wrapped up quite neatly in the informed consent process. You have informed consent from the »



TIM DAVIS
CEO & CO-FOUNDER
EXCO INTOUCH

Mr. Davis co-founded Exco InTouch Ltd, an interactive mobile solutions company delivering innovative mobile solutions for patient recruitment, compliance and real-time data collection in both clinical and commercial settings. Mr. Davis has been a speaker and chairman on the conference circuit since 2000; specializing in the subjects of EDC, e-PRO, implementation of new technologies and electronic source data. He has also written and published several articles around these subjects as well as being a member of the ICR's Special Interest Group on Patient Recruitment.



KARIN COYNE
SENIOR RESEARCH LEADER
UNITED BIOSOURCE'S CENTER
FOR HEALTH OUTCOMES RESEARCH

Dr. Coyne's responsibilities include instrument development and validation as well as design and management of research studies focused on patient-reported outcomes. Areas of expertise include cardiovascular, urology, gastrointestinal, diabetes and women's health. Dr. Coyne has extensive experience in all phases of instrument validation and development.



JACK MCKENZIE
DIRECTOR OF CLINICAL AFFAIRS
PHILIPS RESPIRONICS

Dr. McKenzie is a Senior Scientist and Director of Clinical Affairs, Bend Oregon Division, Philips Respironics Company. He was the Director of the Center for Excellence in Cardiovascular Medicine and served on the NIH, NHLBI, Research Manpower Review Committee and the Training Review Committee. For the past twelve years Dr. McKenzie has been involved in the development and integration of objective ambulatory physiological monitors.



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patient to use their data for what the investigators refer to as medical history, so that is perfectly OK.

That may change in the future if we start to look at electronic medical records and electronic hospital records where we may be accessing an electronic view or extrapolating data directly from an electronic medical record source. With that in mind, that is where HIPAA would potentially come into play. With privacy, I think the models are acceptable, although we are seeing issues in some western European countries around certain sensitive diseases such as HIV, where patients are reluctant to transmit data outside of the borders of their own country. This is one of the challenges we have to accept and it is a matter of staying in touch with the regulatory authorities and helping them with their understanding of the technology.

KC This is certainly a prime opportunity to add in more questions that are related to safety and other attributes about a study that sponsors might be interested in. Make sure the questions, although they might be new, are tested and used in the lay public before implementing on a live scale. This is because you may find that there will be questions that make perfect sense, but once the questions are tested on a larger cohort they are not being interpreted in the way they were intended. When taking any type of question, whether it is part of a standard PRO or just new questions developed for other reasons, it is always good to test in a lay public population first.

CL What new opportunities exist to improve our engagement with patients in clinical trials? New tools? New models?

TD If I gaze into the crystal ball, I think you could look at any sort of disruptive change. There are always economics that play a key factor. We have significant changes coming in economic and clinical trials. We are being asked by the FDA and the other regulatory bodies throughout the world to extend patient monitoring. In clinical trials there will be a Phase II as we will know it, but then the Phase III will become more of an open-label, much larger approach where the tracking of the patient may well extend through the testing phase to the point where there will be a long-term monitoring initiative taken. The key will be finding what platform patients are going to be most comfortable with. Clinical trials will have to adapt and we will see a large uptake in technology.

KC Things will change. They have to change. And certainly technology will take us into the future of enabling longer term follow-up and multiple platforms will have to be used. However, there will need to be consistency within the trial. Technology will have to be consistent so you are not entering random error into your outcomes. I think a Web-based interface — whether on the computer or a PDA tablet in a physician's office or a smart phone — that can be provided to patients is one way you can keep a consistent technology, although with slightly different interfaces. I think there will be a growth in terms of how these are utilized in the future, in how you can provide feedback directly to patients that can help them make decisions and help improve outcomes down the road.

JJ Integration among the platforms that are out there right now. All of the different platforms are being utilized by various sites throughout the globe. The integration of those platforms is crucial for expansion and adoption of technology within the clinical trial industry. The integration that needs to take place between the various devices and different data capture tools that are out there now are really going to depend on the push from regulators. We need to have regulations around capturing this data and making the data work better for the sites, and in turn allowing the sites to work better for the patients.

MF Once we can put the focus on the patient and use one simple interface

with them throughout their life cycle, not just one trial subject lifecycle, then I see that as the future — by focusing on the patient.

JM I think our responsibility as the device industry is to improve ambulatory physiological monitors. I think these have to be transparent devices. Once you put something on a subject, then all of a sudden it is like being watched by “big brother.” We need to develop an ambulatory physiological monitor that is transparent and really blends in with their everyday activities. The other piece of that is the transmission of data has to be in real time. The future is data in real time. Moving forward we need to integrate the physiology with the questionnaires.

CL What changes are needed for us to enable this future?

JM From my standpoint, I really believe education is the most important thing. We need to educate ourselves on: What are the technologies and what do they look like? We need to educate the pharmaceutical world on the potentials they have for measuring whatever it is to make the drug better and to make the measurements of that drug more sophisticated. We really need to educate the FDA on the new technologies out there and what we can we provide for them.

MF The ePRO sector now has a basis by which to work with the regulators and cut down some of the barriers and hurdles. One thing we love about our industry is its consistency, but another word for consistency is inertia. And certainly there is a lot of that in the industry. Anything we can do to work directly with the regulators to remove that fear of change, anything we can do to facilitate doing more accurate electronic methodologies and get better data from the patients, will ensure better patient engagement and quality of both information and treatment.

KC One of the biggest challenges enabling technology integration in the future is working through logistics — working through how to integrate the technology and new processes into the current clinical trial operations; through clinical trial design, through site training, through patient recruitment. Technology affects every facet, and it can certainly make things much easier, but there is a tremendous logistical process that needs to be rethought to accommodate how technology can be integrated into this process.

JJ The driving force of a lot of things we do in this industry comes from the regulators and the FDA. Having the FDA looking at a bigger picture and understanding the scope of the integration that is required to make a lot of these technologies work is critical in the acceptance of it in the future. Not all of the clinical sites are large hospitals or universities, and some of these smaller sites have a great deal of burden put on them when they need to utilize these technologies. Working with the regulators to perhaps certify them as “e-research ready,” or some sort of a process that will enable the sites and investigators to utilize these technologies better, I think really needs to come from the regulators.

TD When looking at this question, I was thinking of EDC as an example of something that had some scale-up. I did my first EDC study in 2000, and at that point a survey was done that said less than 10 percent of clinical studies were done that way. About a month ago, there was a survey that said 60 to 70 percent of studies were done on EDC. I think in an industry that does suffer quite a lot of inertia, that is pretty good progress. I thought about what has driven that uptake? It is really being driven by all the stakeholders realizing this is the way forward. They have seen the benefit, but it has taken eight or nine years to see the positive impact, and how it improves their daily routine. In this second generation, we have to continue to get people to see the technology in action. We have to make sure the sites are happy, and they get their benefits, and that the patients are comfortable and engaged as well. **FP**