Denise Myshko

Data-Driven Patient Recruitment

New tools are being introduced to help pharmaceutical companies identify, screen, and retain patients in clinical trials.

Patient recruitment delays and low-retention rates are key factors in increasing development costs. To optimize both recruitment and retention, there needs to be a plan based on evidence, data, and a set of tools that will work.

Recruiting patients is often a key pain point for sponsors and contract research organizations, says Jonathan Sheldon, Ph.D., global VP, Oracle Health Sciences.

"Companies are looking to advanced tools that make it easier to recruit patients for trials, such as incorporating patient data into a single Health Insurance Portability and Accountability Act (HIPAA) certified environment accessible to both life sciences and healthcare organizations," he says.

The objective of using these approaches and tools is to expedite recruitment of eligible patients in clinical trials and to contain the drop-out rates through widening the reach and enabling pre-selection, says Chitra Lele, Ph.D., chief scientific officer, Sciformix.

"The tools, including commercially available ones, help identify the right patient pool and target the right sites and patients, ultimately increasing the chances of a successful and expedited trial," she says. "The ultimate goal of all these approaches and tools is to optimize the clinical development timelines and reduce the time to market."

The newest tools allow companies to reach people where they are looking for information, says Ritesh Patel, global head of inVentiv Digital + Innovation, the digital consultancy of inVentiv, which works across different inVentiv companies.

FAST FACT

E-PATIENTS ARE 60% MORE LIKELY THAN THE GENERAL POPULATION TO PARTICIPATE IN CLINICAL RESEARCH.

Source: Blue Chip Patient Recruitment

"Patients are not all looking on TV or a newspaper, they are online, talking to each other in forums," he says. "There is a huge growth in patient communities such as PatientsLikeMe, Inspire Health, and Alliance Health. They have vast communities of patients and caregivers who are active."

David Coman, senior VP, marketing, engagement, and communications, Quintiles, says there also needs to be a transformation in the way we think about patient recruitment.

"It's really about patient engagement," he says. "It's not just about recruiting patients and introducing them into studies. It's about how to create an immersive experience for patients that goes beyond just the tactical mechanics of introducing a patient into a trial. This means we have to determine what is driving patient behavior and develop the right mix to engage patients."

Mr. Coman says this involves three things: progressive channels, immersive experience, and progressive techniques.

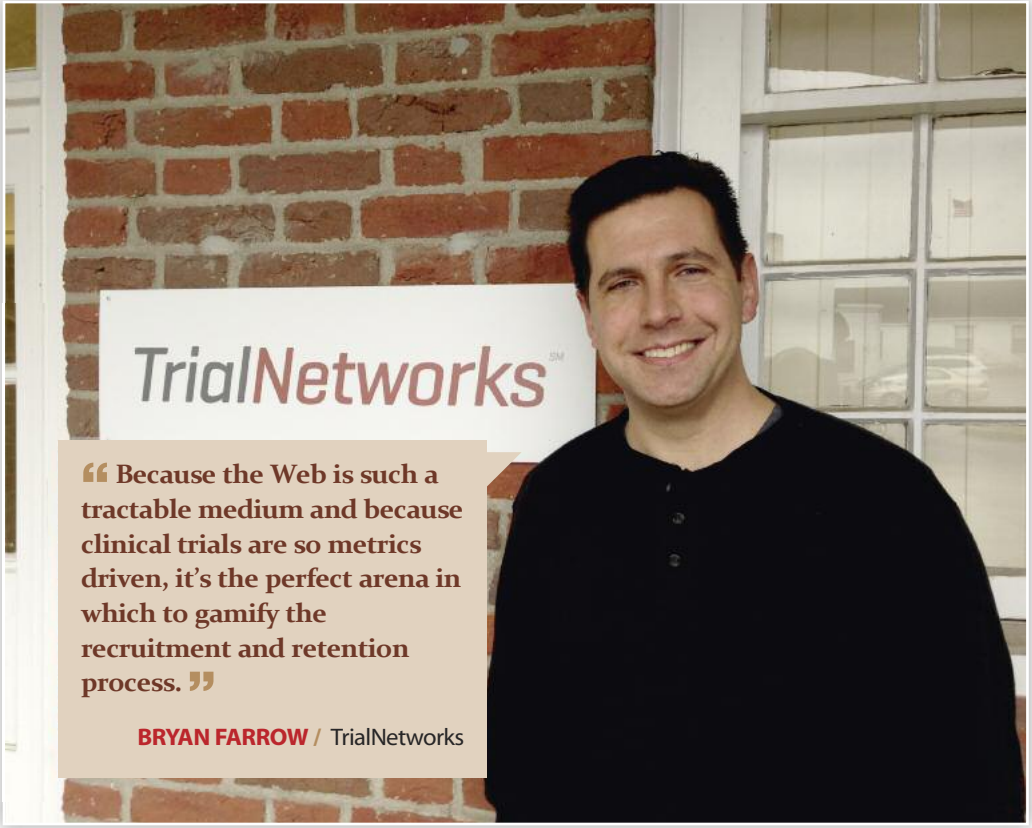
"The traditional form of patient engagement was to enroll a provider and the provider enrolls the patient and the patient has a relationship with the provider," Mr. Coman says. "Today, at the very beginning we are creating touch points to find patients in a branded experience. Every one of those touch points has to leverage core insights about why a patient might want to enroll in the study. We have to create an experience that elicits a sense of purpose. We're trying to create a 360-view of patients as they have an interaction with a provider, a website, and their family and friends throughout the study."

Dr. Sheldon says the goal of such tools is to help healthcare providers and research institutions to collaborate more efficiently with health sciences organizations, with the goal of advancing treatments and improving outcomes.

"Specifically, they help to speed recruitment timelines by collaborating more easily with one or more healthcare institutions and improving decision making by getting instantaneous hypothesis testing results using high quality longitudinal clinical data during protocol modeling/feasibility and validation processes," he says.

Big Data Tools

Recent studies find that the use of big data to inform important decisions is now com-



> **"Because the Web is such a tractable medium and because clinical trials are so metrics driven, it's the perfect arena in which to gamify the recruitment and retention process."**
>
> **BRYAN FARROW** / TrialNetworks

monplace in business but rarely used in clinical trial planning.

Big data allow the industry to look at clinical trials in a very different way, says Liz Moench, president and founder of MediciGlobal.

"For example, you could overlay prescribing data with e-patient search activity to identify the hottest markets that could have been missed when recruiting for a trial," she says. "We have to go where the patients are instead of going to the same wells, which are running dry, and trying to push patients to studies."

She says electronic medical records systems that can be plugged into recruitment and IVRS data will lead to integrated functionalities.

"Data integration is where the focus will be in the next year to two years," Ms. Moench says. "The issue is how rapidly can they be deployed with minimal amount of hands-on implementation. Then those systems have to integrate with other screening and recruitment systems so that you have a complete picture end to end."

A data-driven approach to patient recruitment is increasingly being followed, based on data from electronic health records, patient databases containing anonymized health data, demographic and epidemiological data, historical clinical trial data and secondary data, Dr. Lele says.

"This includes data-driven approaches to protocol feasibility, statistical projections of disease prevalence, and predictive analytics for site selection," she says.

Dr. Lele says while there is a gap in structure and content between data documented during patient care and data required for patient eligibility assessment, EHR data on a patient's age, gender, disease state, and other parameters can be used for an effective screening process with an intelligent selection of patients and patient data.

"The growth of electronic health data is paving the way for a more efficient, scalable method to recruit patients for clinical trials," she says. "Electronic health records form the basis of initial pre-selection of patients. The EHR data can be queried for eligibility criteria using screening algorithms, to expedite the screening process and get to the eligible patients faster."

Janssen is one pharmaceutical company using direct-to-patient techniques in clinical research studies. Quintiles worked with Janssen to enroll patients for a study that aimed to determine which patients respond to a TNF inhibitor for rheumatoid arthritis. To enroll patients in an outcomes-based, Phase IV study, Quintiles collected and analyzed medical records direct from patients to compare patient reported outcomes relative with physician-reported data. Then an invitation and a sample collection kit were sent to patients for biomarker testing.

"Instead of patients going to a lab or a doctor's office, we sent the information to patients," Mr. Coman says. "In the traditional model, the patient burden was to go to the doctor's office, sign paperwork, enter a bunch of data, go to a lab, and there may be multiple visits. Now this is done in the home. The traditional model of having physician investigators who recruit patients took six months to get the first patient enrolled. Using this new model, the first patient enrolled took six minutes. We were able to find 1,000 patients in 18 weeks."

> **"The growth of electronic health data is paving the way for a more efficient, scalable method to recruit patients for clinical trials."**
>
> **DR. CHITRA LELE** / Sciformix

Another company using big data tools is Shire Pharmaceuticals.

"We started to mine electronic health records (EHR) — we have access to 25 million deidentified health records — and we use that data to ask questions related to the patient cohort we are looking for so we don't end up looking for patients that don't exist," says Joseph Kim, clinical operations director at Shire. "For example, if we considered doing a study on pediatric asthma and we wanted to look at the subpopulation of those who have high blood pressure or who are taking drug A and not drug B, we could access those data to make sure those patients exist. Without analyzing a robust EHR dataset, we're left to piece together a picture of how prevalent this population is through key opinion leaders and the literature alone."

Another company, inVentiv Health, also is working with electronic medical records for patient recruitment. The company is working with a network of EHR providers to send clinical trial invitations to patients at the point of care in the doctors' offices.

"There are ways that we could set up with the EHR companies a method or an indicator that would trigger a message that would pop up during patient visits with their doctors," says Jim Carroll, VP, product management, at InVentiv Clinical Trial Recruitment Solutions. "If, for example, a patient is being treated for diabetes and is not controlled with existing treatments, that patient could be offered an opportunity to participate in a clinical trial for patients who are not well controlled using cur-

> "Centralized monitoring of data from EDC and IVR becomes important for retaining patients in trials."
>
> **ERIC SILBERSTEIN** / TrialNetworks

> "Placing clinical trial ads on social media sites is not engaging in social media. That is advertising."
>
> **JOSEPH KIM** / Shire

> "Recruitment involves an immersive experience for patients that goes beyond just the tactical mechanics of introducing a patient into a trial."
>
> **DAVID COMAN** / Quintiles

rently available treatment options. That is another very targeted way we can get a communication to the audience that is going to be much more likely to participate based on their underlying condition."

The company also is with working Adheris Health (also an inVentiv company) to deliver clinical trial invitations to patients on behalf of pharmacies. As a result, the company has access to prescription data across 175 million Americans, Mr. Carroll says.

"We could build a cohort of patients within the prescription databases to understand how many patients are, in fact, available for outreach with a very targeted communication for an invitation to participate in a trial," he says. "We're able to do this in a very unique fashion to patients who meet the clinical trial criteria to see if there is interest. We are able to do that through partnerships with pharmacy chains."

Dr. Sheldon says clinical trial alerts (CTAs) can be generated by EHRs and allow patients to be quickly notified when a trial becomes available that could benefit them.

"This takes the work of selecting participants off of the physician conducting the trial, and further enables patients to select trials that would work for their benefit," he says. "Once EHRs are widely adopted, health data will be much more available to physicians and clinical trial sponsors, making it much easier for them to identify what patients fit the criteria for their trials."

Mr. Patel says countries outside the United States are moving forward with efforts to create a national system of health records that could be used for clinical research.

In the United Kingdom, for example, the National Health Service plans to go paperless by 2018. This will require digital records to be compatible. Interim deadlines include online access to individual records by March 2015 and for all digital information to be fully available across the NHS and social care services by April 2018. This effort could result in £1.7 billion a year being able to be reinvested back into the UK healthcare system, according to a study by PwC.

Mr. Patel says this will likely be more complicated in the United States.

"We have 300 or so different kinds of EMRs providers," he says. "It is very fragmented. Getting consolidated data will be difficult."

In 2013, the National Ambulatory Medical Care Survey (NAMCS) EHR Survey showed that about 78% of office-based physicians used any EHR system. Hospital adoption of EHR systems has more than tripled since 2009, according to a 2013 study by The Office of the National Coordinator for Health Information Technology, part of the U.S. Department of Health and Human Services.

Scott Connor, VP of marketing at Acurian, part of PPD, points out that EHRs still have a long runway before they take off as a truly effective method for patient recruitment.

"These repositories have inherent issues around consistency of the data, privacy concerns, adoption rates and others that are already widely acknowledged," he says. "But the major issue for me is that unless the EHR opens an explicit, direct-to-patient channel to communicate a therapeutically and geographically appropriate trial, it is simply another potential tool to use a proxy for identifying patient populations. EHR/EMR existence doesn't mean that you can contact these individuals directly. Until then, EHRs and EMRs will rely on intermediaries, for example, treating physician who is probably not the PI, to communicate a trial, which effectively removes the power from the patient."

Mr. Connor says the use of electronic data is most valuable for protocol feasibility to the extent that there is the representative data to query with statistical significance.

Dr. Lele says one challenge is that, in most regions, it's difficult to find an EHR system that can be meaningfully used for patient recruitment.

"When EHRs are available, they may not contain all the data required to determine protocol eligibility and the available data may not be complete," she says. "It may also be difficult to write code to effectively query the data if the eligibility criteria are complex. EHR data have to be used in an ethical and responsible manner in clinical research. Ensuring this will require close collaboration between various stakeholders — government, industry, hospitals, patient groups, and technology vendors — and evolution of global standards for sharing health data."

Recruiting Through Social Media

Social media is gaining ground as an important tool to improve the clinical research process through more effective engagement of patient communities, but drug sponsors are proceeding cautiously, according to an analysis recently completed by the Tufts Center for the Study of Drug Development.

Nearly all drug sponsors have developed corporate policies to steer employee use of social media, but the lack of comprehensive, coordinated processes across most organizations

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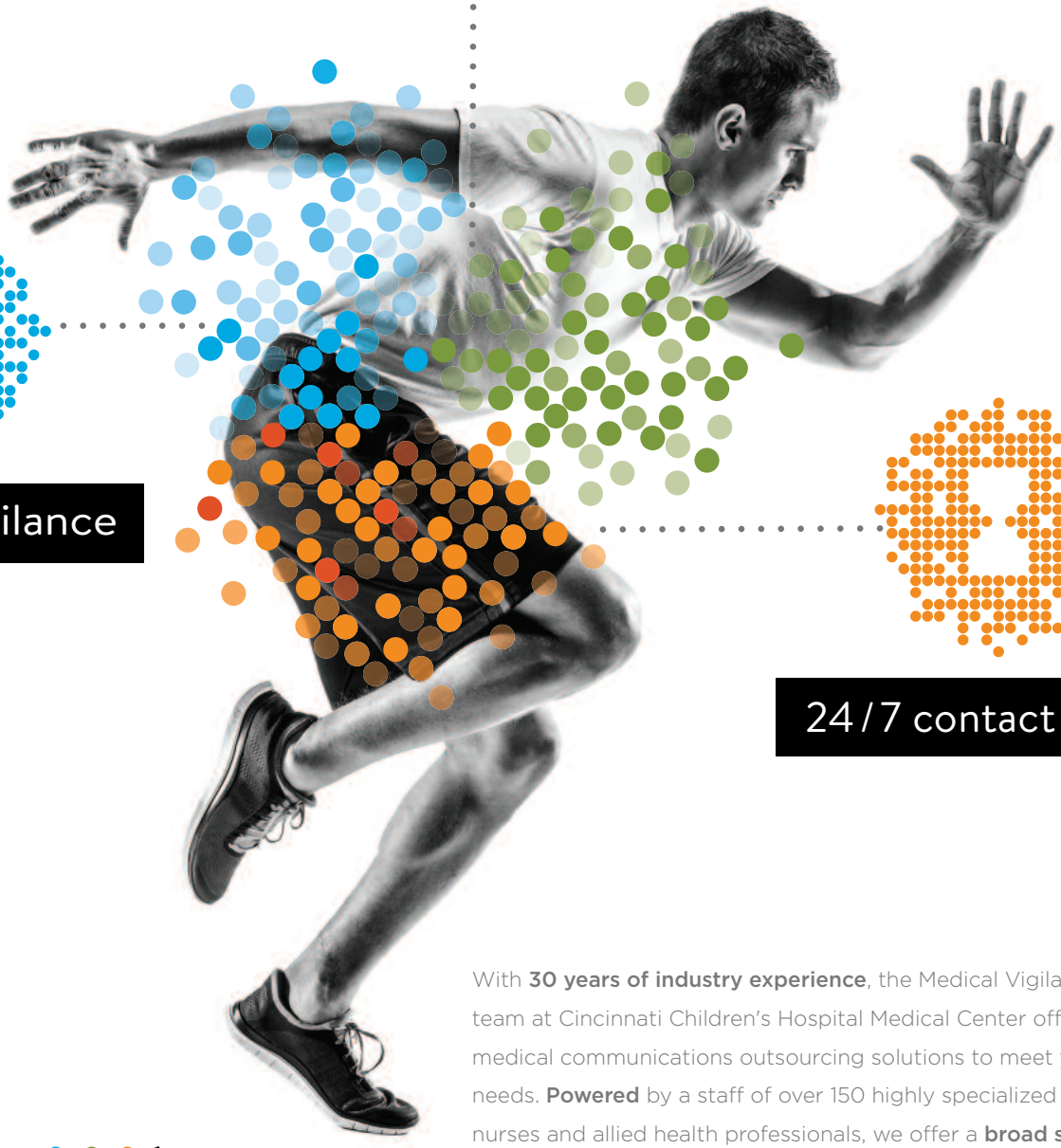

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> "Unless the EHR opens an explicit, direct-to-patient channel to communicate an appropriate trial, it is simply another potential tool for identifying patient populations."
>
> **SCOTT CONNOR** / Acurian

> "The clinical data from EMR systems have to be de-identified based on HIPAA requirements and managed securely."
>
> **DR. JONATHAN SHELDON**
> Oracle Health Sciences

has meant that the companies that are using social media in drug development are doing so in a siloed and experimental fashion, Tufts CSDD found.

Key concerns voiced by drug sponsors about using social media in clinical trials focus on violating patient privacy and confidentiality, jeopardizing research integrity, and influencing study volunteer receptivity to participating in clinical trials.

The use of social media for patient recruitment is fairly limited; in fact, on average companies were using social media in about 11% of their trials, says Mary Lamberti, Ph.D., senior project manager at Tufts CSDD.

"Companies are using Facebook, YouTube, patient communities as well as advocacy groups to spread awareness about clinical trials," she says. "That is more for informational purposes. Companies that are using social media are using it more as a one-way push, and there is not a lot of two-way interactive engagement."

In fact, only one in five companies that use social media directly interacts with patients, according to the Tufts CSDD survey; most contract out engagement to a third-party or use more passive approaches, including placing banner ads on social media sites.

Dr. Lamberti says this is because of unclear FDA guidelines on the use of social media.

"The FDA put out guidance just this year, but that was focused mostly on postmarketing trials," she says. "In terms of using social media for recruitment and retention, there is nothing specific and companies are concerned about usage."

In January 2014, the FDA issued a draft guidance for using interactive media — blogs, social networking sites, online communities, and live podcasts — for approved products. Under this guidance, a company would have to submit materials for FDA review any communication on sites that are owned and controlled or operated on behalf of the company. The agency will take into consideration how much influence the company exerts on the content. If a company collaborates on or has editorial, preview, or review privilege over the content, then it is responsible for the content. The issue of control also extends to its employees when they are acting on behalf of the company, such as a company-directed tweet from an employee's private account.

"In the future, I think there will be more usage of social media, but there are still some challenges," Dr. Lamberti says. "This includes overcoming internal challenges, gaining regulatory approval, concerns about adverse event reporting, and concerns about country specific regulations."

Dr. Lamberti says some companies are beginning to establish governance committees to address some of these challenges and to create a central system to manage and track social media projects.

Mr. Kim says social media can be used effectively but has to be approached differently.

"Placing ads on social media sites is not engaging in social media; that is advertising," he says. "Engaging in social media is about listening and engaging with the audience in an authentic way, in near real time."

Mr. Kim says it's important for pharmaceutical companies to understand how patients use social media.

"There is a good deal of evidence that patients are connecting to each other while they are in research studies," he says. "While patients perceive a benefit to this, they are also unknowingly engaging in some risky behaviors, sharing insights on ways to inappropriately get into research and sharing their progress with each other. Though they are only trying to help each other, this behavior can cause them to harm themselves and the research. For example, they are sharing what the placebo tablets might look or taste like or how to go to a local lab to get blood drawn to see if they are taking active medication. They end up unblinding themselves, which can hurt the science. This will be a runaway train if left unmanaged."

Mr. Kim says ideally it's important to set up some type of controlled environment where patients can connect with each other in a safe way.

"Patients want to connect," he says. "If we don't give people a safe place to connect, they will do it anywhere. Someone has to create a platform so that patients can connect through a social media channel safely. I'm not talking about setting up a Facebook page. I think there needs to be a place that is purposely built for research participants to connect, where there are safeguards built in. Patients also need to be educated about the game of research. I'm looking for partners to help build this for the industry."

Mr. Connor says the best use of social media continues to be IRB- and ethics committee-approved advertising that is placed within social media channels.

"What we have found over the past five years is that social media channels are becoming increasingly nuanced and are capturing more geographically targeted information, which is important to increasing the cost-effectiveness of patient recruitment," he says. "Remember, clinical trial advertising is only cost-effective if you can narrow your reach to specific boundaries around the sites conducting the trial. The other important social media factor is that it has opened the aperture to supporting sites on a more global basis. The worldwide acceptance of online is much greater than traditional marketing methods, both by regulatory agencies and potential subjects. Social media is just one part of that global online equation. It is by no means a panacea, but it does work with the right approach and management.

Borrowing from the Game World

Another new technology for recruitment uses techniques from engagement strategy to recognize and reward people for recruiting milestones.

Because the Web is such a customizable medium and because clinical trials are so metrics-driven, it's the perfect arena for motiving, through quantitative feedback and friendly competition the actions sponsors want to encourage, actions such as enrollment and reten-

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tion of qualified subjects, protocol adherence, and data entry, says Bryan Farrow, director of community engagement at TrialNetworks.

"Because there are a lot of discrete measurable entities in a trial, every time a patient is screened or randomized, that gives us a way to recognize the people at the site level for milestone achievements," he says. "In this way, we are able to recognize individuals for their efforts, which inspires them and their peers to accomplish even more."

Infinity Pharmaceuticals used this strategy for a Phase II oncology study. Working with TrialNetworks, Infinity initiated a 30-day enrollment challenge across all sites in the program. A daily leaderboard recognized sites and awarded virtual "badges" for certain milestones, such as enrolling the first patient. The result was a significant increase in site engagement and ultimately patient enrollment.

"The badge by itself is not what motivates people," says Eric Silberstein, co-founder and CEO of TrialNetworks. "What motivates people is recognition in front of their peers for performing well. This type of program also creates real follow through on the goals."

SOUND BITES FROM THE FIELD

PharmaVOICE asked industry experts about best practices for recruiting and retaining patients in clinical trials.

AARON FLEISHMAN leads the social innovation and advocacy outreach teams at BBK Worldwide.

Today's best practices for patient recruitment and retention are defined by diversifying your strategy, integrating into patients' daily lives, and building a community of partnerships.

We are finding customized mobile applications to be a successful recruitment and retention tool, but traditional tactics, such as television, radio, and Internet continue to prove effective. Simply put, patients' preferences vary. When you focus on the patient and develop diverse strategies that speak to them directly, meeting them where they are, your chance of success will rise dramatically.

It is important to remember that it is not always tools, but people that create the foundation for positive patient recruitment and retention. Involving advocacy groups not only early on, but throughout the lifecycle of a study, actively demonstrates a commitment to providing patients and their caregivers with accessible information from a trusted voice. By making an investment in advocacy outreach, your recruitment and retention will foster awareness and education about clinical research, resonating with patients and empowering them to make better-informed decisions about study participation.

LANCE NICKENS is president of The Patient Recruiting Agency.

Best practices would be: understand your protocol and the demographic profile of the patient you need; understand the implications of the location of your site(s); understand how to effectively budget for recruitment; invest time to select a dedicated, experienced patient recruiting and retention company early; understand potential recruiting and retention challenges and create a plan in advance to increase ROI and reduce the risk of needing a rescue mission; create an effective outreach program supported with the right type of services and tracking/reporting technologies; plan for call handling from patient population for immediate pre-screening; and be forward thinking regarding the right kind of materials needed for the patient demographic.

NEIL WEISMAN is executive VP and general manager at Blue Chip Patient Recruitment.

If you want to meet your clinical trial recruitment and retention goals, there are two essential factors to ensure your campaign is effective and cost-efficient: know your patients and ready your sites.

If you want to reach patients, whether it's through ads, posters, online search, etc., you need to first understand them. What motivates them? What are their aspirations and fears? How does their disease affect their life? What challenges does the protocol pose? Listening to patients, through market research, one on one interviews or social listening tools, are great ways to gather this information. With these insights, you will be able to craft communications that effectively reach and motivate them to respond.

Generating patient inquiries is only the first part of the process. No matter how successful your outreach campaign, sites must be ready to follow up on inquiries in a timely manner. They need to pre-qualify, schedule, screen, randomize, and retain subjects throughout the trial. Sponsors should identify resources for sites to best facilitate recruitment and retention efforts, including easy-to-use systems to track in-practice and outreach referrals, coordinator training, and subject/coordinator tools and motivational programs.

Technology for Retention

Mr. Patel says inVentiv is starting to use mobile apps and text messaging for retention.

"We are now exploring how burgeoning wearable technology can be used," he says. "We are also looking at whether we can deploy live video chat for some studies."

Mr. Carroll points out that regardless of technology, retaining patients in clinical trials requires an understanding of behavior.

"We are using behavioral science to understand patients who have a condition, their motivations and potential barriers, their habits, and how they currently consume content," he says. "That is a research exercise that we undertake very early on in the strategy development process because that helps us to understand the patient and the care team. It is really important in this world of patient centricity that we really understand the full context of the patient and can use that understanding to communicate with patients. Depending on what we find in that research process, that ultimately determines the methods for us to connect with patients based on an understanding of where they are and then also what to use with them to make sure they are staying engaged throughout the trial."

Dr. Lele says there is an enhanced focus on patient retention since the per-protocol subgroup of patients is critical; for example, central statistical surveillance and other risk-based monitoring strategies are used to flag retention issues and customize retention strategies, including use of social media.

Mr. Kim says while there are bright and shiny tools for retaining patients — such as text message reminders and appointment calls — the key is finding out what patients expect and need.

"We really need to understand what retains the patient," he says. "There is data out there on retention, but no one has done a deep dive into why a patient will continue. Naturally, we can assume that some things can turn off patients, such as rude staff, an unclean site, inconvenient hours, and a burdensome protocol. But I believe the real opportunity is engaging patients in the bigger story of clinical research."

Retention, especially in a large trial, is a constant battle, Mr. Silberstein says.

"The approach we take is to get feeds of data from EDC and IVR and look for concerning situations such as a late or missed patient visit or somebody who has temporarily ceased drug," he says. "We have an automated system to assign action items to monitors and sites to make sure that appropriate follow up occurs to prevent issues from escalating. It's a form of centralized monitoring around this very important challenge." PV

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