Patient Recruitment & Retention Newsletter

Special Points of Interest

FACTORS IMPACTING ENROLLMENT
RECRUITMENT INITIATIVES
STUDY/ SITE OUTREACH INITIATIVES
CASE STUDY

JANIX
International Full-Service Contract Research Organization

North America * Europe
Israel * Africa * Asia Pacific

Project Management, Monitoring, Patient Recruitment, Data Management, Biostatistics, Regulatory & Medical Affairs, REMS, Meeting Planning and Wet Lab Set Up & Training

www.JANIX.com

Factors Impacting Enrollment

In our experience early enrollment may be more decisive for the fate of a trial than any other factor. Failing to meet enrollment deadlines is listed as the number one reason why clinical trials and regulatory filings are delayed. Operating as a full spectrum clinical research organization (CRO), JANIX squarely views patient recruitment and retention as a core service and essential aspect of running a successful trial. In undertaking an assessment of the natural history of patient enrollment in a number of randomized efficacy trials, we have examined the predictors determining the ability of trials to reach or not reach their target sample size. In our continuing analysis, many companies and/or CROs do not consistently employ patient recruitment strategies and therefore, lack an appreciation for the fact that early enrollment trajectories will show that the initial rate of accrual largely determines subsequent rates of enrollment, particularly during the first month or two strongly correlating with future rates of accrual.

The patient pool, eligibility criteria, attractiveness of a trial and adequacy of the network of clinical sites are some key factors that influence clinical trial enroll-

(Continued on Page 2)

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Factors Impacting Enrollment

(Continued from Page 1)

-ment. Compounding these factors is the hyper-competitive clinical landscape of therapeutics in development, making access to patients even more difficult. Overall, early enrollment is indicative of the future pace of recruitment and offers strong evidence as to the feasibility of a trial.

Given the critical importance of patient recruitment and its impact on the length and therefore cost of a trial, JANIX has developed a full spectrum of services designed to steer a trial towards meeting sponsor enrollment goals. We believe patient recruitment and retention services are a cardinal aspect of any successful CRO service provider rather than an ancillary or sub-contracted service. Typical CROs either do not appreciate the significant challenge of patient enrollment issues or implement strategies on a reactive rather than proactive basis.

In domestic and international settings, JANIX has implemented the infrastructure, study materials, and outreach initiatives for sponsors to meet trial participation requirements within accelerated timeframes. This newsletter examines in detail and aims to extensively cover general principles, list a diverse array of specific initiatives, present lesson learned, and cover international considerations, case studies, and overall concepts we have employed with confidence to meet demanding enrollment goals.

About Us:

Founded in 2004, **JANIX** is an efficient, metric based clinical research organization (CRO) with a global footprint of operations including North America, Europe, Israel, Africa and Asia Pacific.

Our mandate recognizes the need within the medical research community for quality clinical services backed by experience, ICH/GCP training, protocol adherence, and leadership while offering significant cost advantages.

Representing a vertically integrated and full service Clinical Research Organization (CRO), **JANIX** provides a collaborative and personalized approach to meet sponsor study requirements in a manner that sets us apart from most clinical research service providers.

The key tenets of our business ethos include clear and open lines of communication, sound expectation management, implementation of objective performance metrics, and project accountability at all levels.

Our clients have ranged from big pharma to the emerging growth biopharma, and specialty sector, conducting Phase I-IV clinical studies, and device, registration, marketing, outcomes, cosmetic and nutrition trials.

We've worked with a diverse Sponsor base.
How can we help you?

Clinical Trial Barriers & Promoters

The barriers and promoters identified in clinical trial research span a continuum from awareness to acceptance, and differ depending on the specific population and whether recruitment is for a treatment trial or to a prevention trial. The phase of the study also has a significant impact on attracting patients and in most therapeutic contexts, latter stage trials are preferred by patients relative to earlier phases. This benefit is offset by the increased size of the study population required of later stage studies. Based on a review of various investigations evaluating common barriers and promoters to patient involvement in clinical trial research, the most frequently reported barriers cited across multiple populations are: 1) mistrust of researchers and the "corporate" pharma system 2) the perceived harms of participation in a clinical trial 3) the availability of transportation 4) lack of education about clinical trials and 5) the time commitment required for participation in a trial. The most frequently reported promoters include: 1) patient and provider encouragement 2) altruism and 3) culturally relevant education about trials. Consistent with a broad conceptual framework of evaluating specific clinical trial accrual factors, the barriers and promoters intervene at the level of awareness about clinical trials, the opportunity to participate, and physician/patient interface and the decision-making process about a specific trial. Several studies have presented data on how provider attitudes and perceptions are barriers to and promoters of patient recruitment in clinical trials. Physicians will often state that concerns about patient noncompliance and a lack of available protocols as reasons cited for not talking to patients about clinical trials. Other common barriers include patient age, co-morbidity, and disease stage. Within the range of possible control by PI and sponsor actions, mistrust of researchers and lack of physician awareness about trials as factors that prevented clinical trials from enrolling patients. Other factors include that the provider communication or method of presentation was a barriers where in other studies it was cited as a promoter of trial enrollment. Taken as whole, acknowledging the barriers and promoters to patient recruitment offers a basic starting point to the design, support network required, and implementation of specific initiatives to bolster enrollment.

Taking individual and organizational interests in perspective, the stronger the relationship between sponsor and PI, and the more thoroughly vetted prospective candidates are selected, the higher probability a trial will obtain the energetic support of sites and investigators for successful enrollment.

Starting With Physician Support

Clinicians form relationships with patients and play an influential role in advising patients regarding participation in a trial. However, they often have limited awareness about opportunities to participate in trials, the trials may not make sense to them from a fiscal point of view, and for certain patients, some providers have serious concerns about the risks of participation in clinical trials.

Ultimately, like patients and individuals at risk for a disease, healthcare providers base their decisions on the balance of risks and benefits of trial participation. Although seemingly obvious, these barriers to recruitment are often overlooked though they are easily mitigated through study support campaigns that use basic informative marketing strategies.

Taking individual and organizational interests in perspective, the stronger the relationship existing between sponsor and principal investigator, and the more thoroughly vetted prospective candidates are selected, the higher probability a trial will obtain a greater level of energetic support of sites. Here again, given the heterogeneity of clinical practice contexts, intervention strategies for the enhancement of patient accrual must be adapted to this context and have a high likelihood of being sustainable.

"raising concerns about futility: Is it legitimate to continue a trial when its enrollment pattern predicts it will most likely be unable to reach its target?"

Factors Impacting Enrollment

Evidence suggests that the age of the patient population, trial domain or masking will affect the final ability of a trial to accrue its target. There is concern that double-blind placebo controlled studies may be less attractive to patients' participation, but empirically overall double-masked studies will reach as much of their target as unmasked ones. Predominately it is the patient pool, eligibility criteria, attractiveness of the trial protocol and adequacy of the network of clinical sites that are regarded as some of the key factors that influence clinical trial enrollment. Therapeutics in development also may have direct competitors, whether different compounds with similar MOAs, varying administration routes, or off label studies, etc. In a 2001 analysis of 77 HIV randomized clinical trials, most of the trials that had slow early enrollment did not reach their target sample size (80%) and more than one-half of them lasted longer than a year and some even several years. This raises concerns about futility: Is it legitimate to continue a trial when its enrollment pattern predicts it will most likely be unable to reach its target, especially if resources for clinical research are limited showing the correlation between very early and late enrollment parameters. It is within this context that patient recruitment and retention initiatives are implemented as a direct means to mitigate a potential slow enrollment trajectory.

"Failing to meet enrollment deadlines is listed as the number one reason why clinical trials and regulatory filings are delayed."

Basis to Patient Recruitment

"patient recruitment activities starting after the investigator meeting or when enrollment flattens – is often too late to make a significant impact"

It is clearly evident that the faster the early enrollment, the more likely a trial will reach its target sample size. As previously noted, some of the inherent challenges of enrolling a trial derive from the epidemiology of the disease and steadier prevalent patient pools, the competitive landscape of other pharmaceuticals in clinical development, and the power of the study in terms if total required patients. In general, patient recruitment activities should be implemented at the same time site recruitment is occurring. Our philosophy maintains that when patient recruitment activities start after the investigator meeting or when enrollment flattens – it's too late to make significant impact. A North American Study found more than 90% of all clinical trials had to extend their enrollment period significantly beyond the required project timeline. In another study of 163 phase III clinical trials, 78% failed to complete on schedule . For a drug destined to make $500M in annual sales, a one-day delay can cost up to $1.3 million ($40M per month). Adding insult to injury; direct costs of a phase II clinical trial will often run between $1-2 million per month. There are numerous patient recruitment and retention techniques, many of which we have independently developed and validated. Of particular importance is that no set rubric or temporal deployment of tactics exists, what works for one trial at a certain time in the progression of the study will not necessary translate to another trial. Rather, a unique set of circumstances will lend themselves to implementation of initiatives and generally, multiple strategies are run in parallel. There exists a number of core patient recruitment approaches that are best implemented prior to commencement of a trial. During this formative stage generation of the foundational strategy including implementation goals set forth in Gantt charts to define key supportive efforts aimed towards bolstering enrollment.

Enrollment Initiatives

Outreach Services

- Physician Dinners
- Physician Mailing
- Physician Email Campaigns
- Speaking Engagements
- Chart Review Support Services
- SC Telecons
- Web Training/ for Physicians

Recruitment Initiatives

- Set Up Patient Recruitment Specialist Program Presentations to Sites
- Poster Presentation Program
- Transportation Program
- Clinical Trials Branding Strategies
- Comprehensive Market Research
- Study Awareness Building
- Mixed Media Advertising
- Call Center Services
- Physician & Community Outreach
- General Site Support Services
- Performance Metrics Analysis
- Establish Study Revitalization and Rescue Options

Trial Reference Materials

- 3-Month Recruitment Activity Calendar
- Recruitment Brochures/Posters
- Pocket Protocol
- Chart Identification Stickers
- Study Participation Alert Notice
- Pre-screening Worksheet
- Study Visit/Roles Reference Packet

"Encourage sites to maintain open lines of communication and to share information of best practices to other sites involved in the study"

Patient Recruitment Workshops

Organizing patient recruitment workshops and sharing how to develop a site plan of activities encompass leveraging a PI and impressing the need to achieve patient enrollment goals. This also includes making sure site coordinators are privy to the key initiatives and how to augment initiatives already in place. One key forum for sharing patient recruitment strategies is during the first investigator meeting. Investigator meetings allow for CROs and sponsor representatives to present the fundamental tenets of the patient recruitment strategy for the trial. Often it is important to arrange for guest speakers who command respect for not only knowing the core aspects of the clinical study but that can also encourage support for the patient recruitment strategy set in place. It is essential to build in time during the investigator meeting to involve the regional CRAs to work in lockstep with the principal investigator and study coordinators and to generate a site specific plan based on unique demographic factors or alliances the physician may have that can positively impact enrollment. Also encourage sites to maintain open lines of communication and incentivize them to share information of best practices to other sites involved in the study, encouraging a teamwork approach to completing the study.

Highlight The Science

It is imperative that the essence of the science be conveyed, after all the primary goal is to develop innovative therapeutics designed to meet unmet medical needs. Physicals and nurses alike will support a program to a greater extent if they appreciate the more elegant scientific studies in support of a therapeutic agent. Speak with fervor as to the scientific basis in support of the therapeutic and the lengths to which product development minimized side effects. By utilizing journal articles, abstracts, posters, press releases, PowerPoint presentations presenting key aspects of the investigator brochure, mechanism of action outlines, and various documents that capture the historical body of evidence that supports a therapeutics treatment potential.

Pooling Resources

Other methods of disseminating information particularly with respects to significant events such as newly published journal information to site personnel include teleconferences and web conferences. It is also helpful to utilize CRA resources and provide template telephone contact reports, site visits, and ongoing meetings. Incentive CRAs by aligning bonuses with meeting key enrollment benchmarks and provide them with the resources to contribute to finding potential new patients. Another key source of adding new patients is via physician referral networks. Encourage referral of patients from neighboring physicians. Provide a sponsor approved template letter describing the trial and instructions on referring patients. Items to include would be checklists for the MD and IRB approved material for patient distribution. Encourage the investigator (with CRO assistance) to generate a list of their colleagues in the field (within their medical center, neighboring medical centers or clinics, etc.) who would be open to referring patients. It is also of value to obtain Local Physicians' addresses and contact information from website searches and/or from Medical Associations.

Physician to Physician Referrals

You may also want to expand the therapeutic area, especially if comorbid or varying disease states are associated with the target indication i.e. patients suffering from a constellation of sequelle with subspecialties involved in treatment. Referrals via primary care or family physicians can also allow additional leads for candidates. Tap into ICD-9 codes via a physician's billing records for past diagnosis that may be applicable. Email or mail the sponsor approved "Physician to Physician" letter to your newly identified referral network of physicians. These tasks can be performed in-house or require the CRO to take the lead if a high degree of confidence exits in their ability to execute such initiatives and follow through. Be conscious to the fact that many positive effects on enrollment rates are often latent but will come to fruition if supported.

Calling Campaigns

Leveraging telephone campaigns entails a number of actions that are both cost effective and provide additional momentum during trial execution, including:

- Telecon with all Study Coordinators (or persons responsible for patient recruitment at the study site) to "Brainstorm" on best practices.
- Utilize staff with a robust understanding of the medical merit of the study contact sub-PIs.
- Generate a Calendar of Patient Recruitment strategies for the first 3 months of enrollment for consideration.

Aspects unique to PI calling campaigns and some considerations include:

- When to Call
- Who makes the Calls
- Frequency of Calls
- Script of Calls
- Division of Sites for the Calls

Enrollment Initiatives

With respects to internal staff a variety of techniques and establishment of a strong working relationship will directly benefit patient enrollment. Specific examples include the following:

- Inform all relevant site personnel who could assist in identifying potential patients (In-Services, RNs, Other practitioners, Billing, etc.).
- The PI/Sub-I can train department staff by using Sponsor approved slide presentations as a tool to explain the basic science and protocol rationale.
- In addition, a breakfast or luncheon where fellow site coordinators and sub investigators can assemble to receive training on the trial may be beneficial.
- Laminated Pocket Cards containing the eligibility criteria, procedure chart as well as the eligibility check-list and other helpful information
- Study staff are encouraged to keep Pocket Cards with them at all times so they can refer to them when seeing their clinic patients. Physicians and site personnel can also utilize them when on-call at the hospital.
- Eligibility criteria can be down loaded into iPhones, Blackberrys, Phones, Computers, etc..

"A North American Study found more than 90% of all clinical trials had to extend their enrollment period significantly beyond the required project timeline ."

Site/Study Outreach

- Physician Recruitment Brochure
- Patient Information Pamphlet about Disease of Interest
- Recruitment Poster for Office
- Print/Radio Ad
- Pocket Protocol
- Eligibility Cards
- Chart Stickers
- Pre-Screening Worksheets
- Alert Stickers
- Study Reference Cards
- Patient Support Tools (ensure PhRMA Guidelines are followed)
- Local Events/ Patient Outreach
- Local Support Groups
- Local Charity or Fund Raising Organizations
- Post IRB approval information within clinic, or other appropriate places

Clinical Meetings and Conferences

Society Meetings are an ideal setting to gain support.

- Outside Resources – Present main study synopsis and main eligibility criteria to colleagues to increase awareness.
- Therapeutic Area Society Meetings
- Specialty Area Society Meetings
- Any applicable conference
- Physician Awareness Dinners - Facilitating Face to Face Interaction is KEY!
- Search the internet or other local resources to identify appropriate medical meetings in which the PI or other MDs can present the study to colleagues to extend interest. Physician dinners can be arranged locally.
- In-Service Training meetings can highlight study criteria and foster study awareness.

Case Study—Expedited Enrollment

JANIX was awarded a struggling program a year after initiation that was well behind enrollment expectations due to several factors, including a hyper-competitive industry pipeline and difficulties in patient recruitment due to the semi-invasive administration route of the therapeutic. As enrollment became more critically behind benchmarks the sponsor began to add international sites one after another, activating a new country as quickly as possible and relying on multiple CROs to mitigate risk. Many of the countries they added simply didn't produce. This was a result of the inherent challenges previously noted and further compounded by a rare patient population and the requirement of difficult certifications prior to site activation. Once formally scoped to the project and after a fairly quick due-diligence period, JANIX implemented a full complement of patient recruitment strategies and certification workshops during the site recruitment phase of the new regions and sites assigned. In this scenario JANIX was managing 13 of a total of 121 global sites, approximately 10% of all active sites. Our results, largely driven by an approach that squarely viewed the positive impact patient recruitment strategies was contributing 38% of total global enrollment by the close of the trial. This provided clear cost savings as 10% of sites contributing to almost forty percent of total global enrollment is of immense success. Overall, a vigilant approach to leveraging patient enrollment mechanisms earned JANIX subsequent studies from the sponsor and a lasting partnership.

JANIX

International Full Service

Contract Research Organization

Your Prescription for Clinical Research Success (SM)

As an international full service contract research organization (CRO), JANIX supports a wide range of activities unique to clinical research including management and monitoring, data management, biostatistics, medical and regulatory affairs, patient recruitment and retention, and a host of other important services, for Phase I-IV studies, and device, registration, marketing, outcomes, cosmetic and nutrition trials.

Our Full Service Menu Includes:

- Project Management
- Clinical Management
- Monitoring
- Patient Recruitment & Retention
- Data Management
- Biostatistics
- Regulatory Affairs
- Medical Affairs
- Device Surgical Wet Lab
- Investigator Meetings
- Advisory Board / KOL Meetings
- 24/ 7 Travel Agent Support
- Phase I-IV Bio/Pharma Studies
- Device Studies
- Registration Studies
- Marketing Studies
- Outcome Studies
- Nutraceutical Studies
- Cosmeceutical Studies
- Risk Evaluation & Mitigation Strategy (REMS)

"In an analysis of randomized clinical trials, most of the trials that had slow early enrollment did not reach their target sample size (80%) and more than one-half of them lasted longer than a year and some even several years after projected close."

WE'VE WORKED WITH A DIVERSE SPONSOR BASE. HOW CAN WE HELP YOU?

JANIX: International Full-Service CRO

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