Proactive Planning for Subject Recruitment and Retention are Critical to Modern Clinical Trial Success

PEER REVIEWED

Despite countless industry efforts to improve efficiency in the planning and execution of clinical trials, 80 per cent of studies are delayed in their completion by a third or more of their intended durations[8]. Protracted study delivery has staggering financial and clinical implications for both biopharmaceutical companies (lost revenues of $8 million per day delayed[8]) and the patients they serve. The Manhattan Research Institute has developed a formula showing that a setback of just one year in availability for new drugs for AIDS/HIV, breast cancer, and non-Hodgkin's lymphoma alone is estimated as costing $27 billion[31]. Achieving enrolment milestones can literally be the sole determining factor in the survival of small biotech organisations with only one or a few therapies in their pipelines. For many patients, it is literally life or death[4].

Patient enrolment, or lack thereof, is frequently cited as the primary reason for clinical trial delays. As such, there is growing fervour for the implementation of robust subject recruitment and retention initiatives in research studies. The widespread adoption of new technologies and services, such as social media, electronic medical records (EMRs), and remote data capture, brings many opportunities to boost protocol participation, but also introduces many new challenges. The key takeaway for today's study environment is that subject management, from pre-screening through study completion, must be carefully planned and closely supervised; it cannot be taken for granted to proceed on its own[1]. And even with technological advancements, the industry cannot underestimate the importance of interpersonal relationships[30].

Recruiting the Modern-day Patient is a Difficult Task

There is widespread interest in clinical trial participation with 94 per cent of the public agreeing that research involvement is "very important to advance medical science"[5], and similar metrics support research and its funding in general[8]. When it comes to actually recruiting clinical trial participants, however, the industry is facing an uphill struggle. A 2008 survey revealed that only 17 per cent of 1000 respondents believed clinical trials to be "very safe" and 14 per cent revealed that they had no knowledge of the topic whatsoever[8]. Seventy per cent of those questioned for a recent industry white paper indicated having no awareness of the most common online clinical trial databases (e.g. ClinicalTrials.gov)[12], further sustained by 74 per cent admitting "no 'real' knowledge of the clinical research process" and nearly everyone stating they don't have the tools to appropriately evaluate potential studies[5].

With the proliferation of online communication methods, the rapid expansion of social networks, the "always-on" 24-hour news stream, and expanded access to mobile media, we are inundated with data at a pace never before seen. The typical person is exposed to the equivalent of an entire novel's worth of information every single day[6]. It should come as no surprise that even the most targeted messages may get lost in the fold. Despite uptake of social media, its use for engaging patients is still in its infancy due to privacy concerns and lack of proper guidance from regulators. After years of debate, the FDA's initial draft guidance issued in December 2011 for patient-initiated requests arrived with no clarity as to what may be allowable regarding engagement via social media outlets[14].

Still, figuring out a way to use these newer media in a targeted and acceptable way is a potential boon for clinical research. In May 2011, 179 "e-patients" – those who rely on social media and online networks for health information – revealed that they more consistently visit a doctor, are more apt to adhere to prescribed medical schedules, and are 60 % more likely than the general populace to have participated in a clinical trial[12]. Interestingly, this same survey showed that the vast majority – 80 per cent – read information available on healthcare websites and social networks, but are not necessarily inclined to post content in response; thus a successful social media campaign cannot rely on self-reporting from potential subjects. It is up to the industry to get the word out via these alternative venues.

Where social media shines is in its ability to reach those with similar, often unique or orphan conditions or circumstances[13]. Tapping into networked communities of those with rare diseases and/or similar life situations gets directly to the populations of interest for trial recruitment. By advertising or otherwise engaging in these communities, sponsors, CROs, and sites alike can reach a ready pool of potential subjects guaranteed to meet basic study criteria. Considering a broad definition of social media, there are dozens of focused and immediate opportunities with topical communities like PatientsLikeMe and the Fox Foundation's Fox Trial Finder[10,23,15]. On PatientsLikeMe, for example, users can enter their conditions, gender, age and location to find relevant clinical studies nearby. From the investigation side, reviewing a specific ongoing study shows the number of registered PatientsLikeMe users who may

qualify based on their profiles. Registered users are able to directly interact by drilling down through other registered users' profiles, making direct contact between researcher and potential subject simple, though perhaps a bit invasive when done improperly[23]. With a lack of regulatory guidance, it is left to sponsors to work with IRBs in determining the most appropriate means to engage patients in this fashion[25]. But if sponsors advertise or otherwise promote their trials in like communities, they have an immediate leg-up in gaining the attention of the high-value "e-patients."

Yet all this talk of social media is not without its complications. Pfizer's much-ballyhooed REMOTE study, designed to be entirely technology-driven with social media at the core of the recruitment strategy, was terminated prematurely in June 2012 due to lagging enrolment[11]. Rahlyn Gossen – a former research coordinator who now runs RebarInteractive.com[26] which explores advancement of new means of recruiting trial patients – is firmly committed to digital methodologies, yet she remains equally critical of social media's potential, particularly because of the long-term commitment needed to make venues like Twitter successful[22]. She suggests that social media today can most effectively be used to increase awareness and build rapport by creating original content and getting the word out through channels like YouTube[24]. Gossen sees this as a developing area as effects of traditional media wane[22]. So social media may very well be a means to augment, rather than revolutionise, patient accrual at the current juncture.

As a less progressive but more immediately accessible technology, increasingly routine use of electronic medical records (EMRs) provides an excellent opportunity to quickly and efficiently scan patient data that were entirely inaccessible or severely cumbersome to navigate in their previously disparate state. Use of EMRs has already shown promise to accelerate research recruitment[28,3]. As demonstrated in a 2011 general practice study in Germany, implementation of a study-specific "clinical trial alert" tool allowed site research coordinators to partially automate the patient identification process, such that they combed through over 16,000 potentially eligible EMRs in order to contact nearly 2000 patients leading to over 1500 enrolled subjects[29]. This type of rapid, automated screening process would not be possible in the 'paper world.' Pre-screening EMRs for potential patients has additional added benefits of confirming the viability of a potential study as described in Case Study A (see inset).

It should be noted that the proliferation of technology on its own cannot resolve the entire recruitment challenge. Given the intimacy of healthcare information, trust is primarily achieved through credibility and respect for privacy that can only be offered from physician interactions; transparency is paramount to success[9,12]. Patient recruitment agency Blue Chip suggests that, when considering social media as part of the accrual strategy, it is important to ensure demographics of the study requirements and the targeted communities are well-aligned, that transparency is actively maintained with involvement of a physician, and that information is timely, accurate, and readily available for sharing within or outside the target forum[12]. A 2012 meta-analysis further confirms that direct physician involvement in the design and recruitment of studies is the single most important criterion in successful enrolment[16].

Similarly, though it may seem obvious, proper site selection by sponsors and CROs can be the ultimate determining factor in successful recruitment. Retrospective analyses by Pfizer and Lilly have shown, perhaps not surprisingly, that strong site performance on a prior study is the most important factor in likelihood of recruitment success on a new study. This is even further amplified when investigator experience is taken into consideration[17]. And when other factors influence the start of a trial, as in Case Study B (see inset), additional effort is required to ensure recruitment proceeds as planned.

Recruitment is Not the End of the Line

With intense industry focus on means to bolster study accrual, patient retention often goes without planning. It costs significant capital – financial, temporal, labour, opportunity cost – to enroll each trial subject, so keeping them on a study through completion is equally as important as the initial recruitment. There will always be the unavoidable loss of subjects – unrelated adverse events, relocation, co-morbidities – so there is good reason to make certain that, barring medical reason, subjects are encouraged to remain on study. This requires creativity, flexibility and real commitment from the sponsor and the trial site.

One means of helping to retain the modern-day study subject is via the reduction of in-office requirements. Though Pfizer's REMOTE study as discussed previously may be considered a disappointment as relates to enrolling subjects, the entirely decentralised patient-centric approach with minimal intervention from trial investigators demonstrates maximal flexibility for the modern-day study subject. Trial participants have been able to complete all their data reporting via electronic patient-reported outcomes (ePRO) tools, regardless of trial site proximity, and have been able to reach study physicians 24 hours a day to discuss participation. Whether a fully virtual trial is 'science future' or 'science fiction' remains to be seen, but certainly some of the tools, including expanded collection of remote data, is a growing trend to improve study speed and subject retention and compliance[21]. Sponsors need to be creative and flexible in acquiring data, particularly for long-term or highly involved studies so as to minimise disturbance of subjects' everyday activities with commitment to patient convenience[20,27].

As evidence of this, utilising 'in-home' study visits is another means of boosting patient retention, particularly for studies that require lengthy or frequent procedures or data collection. For example, a study nurse may visit trial participants in their homes or offices to collect blood samples or administer IV dosing, rather than requiring a subject to travel to a study site. Not only is this a

significant added ease for trial subjects, but it has the effect of fostering a stronger bond between participants and the trial care-givers, thus improving long-term retention[20]. In a case study published by Symphony Clinical Research, dropout rates across multiple Phase II/III two-year orphan drug pulmonary studies were reduced from two-thirds to just three per cent with addition of homecare services. For those planning new studies, use of decentralised patient care may be a useful and cost-effective tool in certain situations to reduce participation burden and thus improve long-term retention[7].

Interestingly, whereas recruitment is evolving to include more technology-driven concepts, retention may be enhanced through significantly less evolved methods. Research shows a direct correlation between the level of involvement of the principal investigator, the approach and attitude of the research nurse, and the level of empathy for the trial subjects[19]. So though these facets may be perceived as less controllable by those managing studies, employing a high level of site education and training with a concerted focus on patient-centric ideologies may be the most effective means to ensure subject retention.

Finally, in cases of long-term studies, use of retention specialist organisations may significantly improve outcomes. In one example, an HIV study which had lost over 25 per cent of participants after six months was able to re-engage nearly 90 per cent of those lost subjects using concentrated outreach efforts, suggesting again that planning for retention is a necessary part of overall study planning[2]. Case Study C (see inset) explores a solution used to maximise patient retention over a long-term study.

Applying Lessons Today

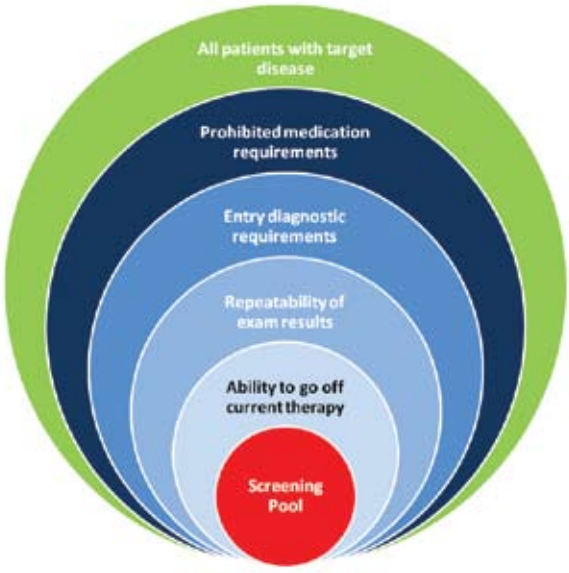
All told, the actionable lesson from this is that it is critical that sponsors, study investigators, and clinical monitors assess the specific qualities of each protocol and site in order to customise the best approach to recruit and retain for each given circumstance; there is rarely a "one-size-fits-all" solution to successfully enrolling and maintaining trial patients. Perhaps the most important consideration for a multisite protocol is recognition that each site will have its own unique needs, and that all stakeholders need to collaborate with each sites' investigators and coordinators to define and implement an appropriate strategy[18]. Investigators' direct involvement starting at the consultative stages is key to gaining patient buy-in. And the quantitative effect of all strategies needs to be continually assessed and recon d as the trial proceeds. Like most parts of research, subject management is a "living" process that starts and ends with humans[1], and planning is essential.

The rise of social media and increase in "crowd-sourced" engagement bring new avenues to interact with and gain attention from potential and enrolled trial subjects. But use of these and all media has to be carefully planned in order to meet the rigours of ethical and regulatory guidelines, as well as to gain the trust and acceptance of the broad population. Planning, monitoring, and reacting to subject recruitment and retention trends, are critical to ensuring trial success[27]. In the end, recruiting and retaining research subjects are very human endeavours, and relationships matter. Planned efforts have never been more challenging, more creative, or more necessary, and are only going to continue to evolve.

CASE STUDY A - Electronic medical records (EMRs) to pre-screen for specific protocol requirements are a useful tool to pre-select study subjects and assess protocol viability even prior to initiating a trial.

A scientific roundtable was convened to finalise protocol development for an untried novel therapeutic approach. Many study design elements were assessed including prohibited medications, diagnostic requirements for enrolment, number and frequency of various study assessments and specific inclusion / exclusion criteria. There was general consensus among the research experts that the agreed elements, taken individually, would have minimal impact on the 'enrollability' of the study. To confirm this, the CRO enlisted three investigative sites to review their EMRs based on eight specific criteria proposed for the protocol. The results were self-evident: at best, only three per cent of patients with the target disease may initially qualify for screening. The protocol was essentially not viable in its then-current form. This inexpensive and quick appraisal demonstrates the power of EMRs and value in quantifying enrolment potential before investing significant human and financial capital. Without these results, this trial would have failed as planned, and the protocol amendments required mid-study would have significantly delayed the timelines and degraded investigator and subject motivation.

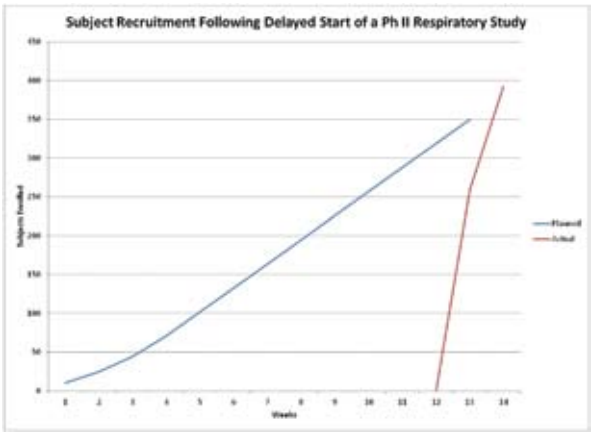
Figure 1 – Protocol criteria may seem insignificant when considered individually, but as a whole, may greatly reduce the screening pool of target subjects.



CASE STUDY B – Implementing multifaceted motivation and recruitment campaigns saved a Phase II respiratory study from significant delays.

Initiation of a Phase II respiratory study had to be halted due to manufacturing issues just one day before screening was scheduled to commence. The sponsor and CRO immediately recognised the importance to proactively manage expectations for all stakeholders in order that the delay not become crippling. A mutual agreement was negotiated to ensure that the fully-trained CRO team remained intact and, working through the clinical monitors, there was immediate, transparent, and continuous communication to the sites about what was going on. The management team used the delay to develop and gain IRB approval for print and radio marketing tools placed locally near trial sites. The sponsor conducted direct outreach to each principal investigator and the CRAs conducted routine check-ins with the study coordinators to keep motivation high. Sites were provided with pre-printed postcards with information about the study that were sent by the hundreds to potential study subjects. Just prior to reopening the study, refresher phone initiations were conducted with all sites. In recognition of additional prescreening efforts, sites were each paid an additional non-refundable retention bonus when they screened their first subjects. The significant efforts paid off when the trial started twelve weeks behind schedule and subjects were literally lined up to be consented. The expected recruitment period was condensed from twelve weeks to just eight days and the trial overenrolled. The transparent communication and additional emphasis on recruitment efforts helped build site rapport, maintain interest and trust, and create an environment of excitement at a time when circumstances may have otherwise had the exact opposite effect.

Figure 2 – Despite unplanned delays to initiate a Phase II respiratory study, proactive measures allowed subject recruitment to complete rapidly.



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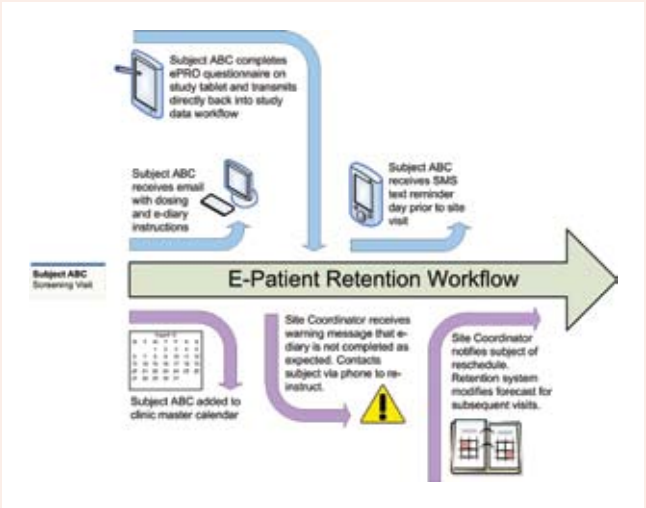
CASE STUDY C – Use of automated forecasts and visit tracking aids study retention efforts.

For a large multisite vaccine study, the CRO and sponsor employed an electronic tracking system whereby, once a subject's initial screening visit was entered, a full forecast of subsequent visits was generated. This allowed sites to print calendars of upcoming activities for use in their clinics and to be included in patient charts. The system also generated automated email and SMS text message reminders to study coordinators and patients in advance of scheduled visits, and as notifications for when projected visits had not been registered. To implement such a system, direct-to-patient communications needed prior approval from ethics committees, and participation was described and approved via the informed consent process. Though not used in this case, careful planning may allow additional automation via integrations with randomisation and/or EDC applications for added notification capabilities. Patients and site coordinators agreed that this approach added significant value in aiding a busy time management process.

Figure 3 – An electronic patient retention system provides automation for scheduling activities resulting in improved compliance and added convenience for study subjects and research coordinators.



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email: sales@pdpcouriers.com
www.pdpcouriers.com

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Nicholas Spittal, MBA, PMP, Director, Strategic Clinical Development at Chiltern International, has been directing multi-national clinical research studies for more than ten years in difficult-to-enroll populations, including the then-largest programs in three different ophthalmic indications. Chiltern International is a global full service contract clinical research organization offering consultation and drug development services to the biopharmaceutical industry. Mr. Spittal may be reached at **Email: nicholas.spittal@chiltern.com.**