Pharma-Search Ltd.

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PATIENT RECRUITMENT

A CHRONIC DISORDER FOR THE PHARMACEUTICAL INDUSTRY

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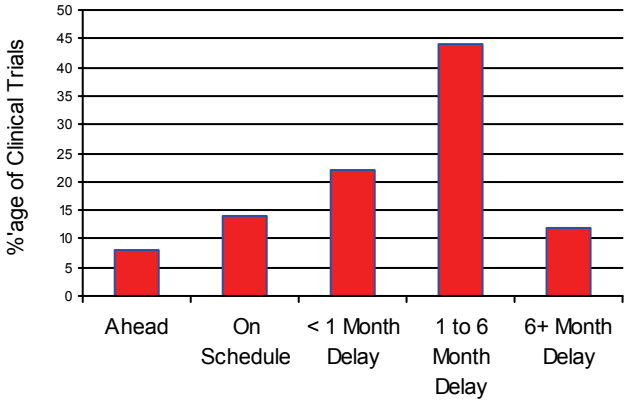
WHAT IS THE PROGNOSIS? IS THERE A CASE FOR PREVENTION, CURE OR IS IT TERMINAL?

Patient recruitment remains the biggest single source of delay for clinical trials programmes, and costs the industry hundreds of millions of dollars per annum.

The number of patients in a new drug project has increased from about 1,300 in the early 1980s, to more than 4,000 today and looks likely to continue to rise if current trends are bourne out. With that in mind the industry is set for a shortfall in investigators (and therefore patients), estimated to be about 15% in 2006.

In the United States there is an estimated cost of patient recruitment of US$1.9 billion, just under 30% of the annual cost of clinical trials. The costs escalate with every day that the product does not reach the market, linking every day lost in development of a blockbuster, to in excess of $1 million in lost sales. With over 50% of all delays attributed to patient recruitment problems and over one quarter of all investigator sites failing to recruit a single patient, there is a critical need to address the issue of patient recruitment.

The situation is made all the more acute by the requirement for increased patient numbers against reduced time lines. Patients are notoriously reticent to put themselves forward for inclusion into clinical trials. They often mistrust the industry and its intentions and the recent explosion of information available on the internet has only increased confusion and doubt.



Patient recruitment is becoming increasingly competitive, with more companies looking to secure patients from a decreasing pool. It is estimated that within any given disease area, a maximum of 5% of patients agree to participate in clinical trials. So, how can the industry identify, attract and recruit more of the majority, i.e. 95%, of patients to their trials?

Pharmaceutical companies are beginning to address this issue through a number of routes:

Feasibility and managing expectations appropriately e.g. Assessing disease incidences within a given population or geographical region. Understanding the cultural diversity that may exist and how this may impact the trial. With any given move to a specific location, understanding the local regulatory issues that may further hinder patient recruitment.

These measures will initially be time intensive, but assuming that the data is collected, collated, analysed and stored appropriately, it will allow for a positive impact and return on the investment. Ultimately the more precise this data is and the more frequently the right questions are being asked, the more confident one will be that the trial is being initiated with the highest probability of success in recruiting the required patients into the study.

Many organisations are still writing protocols with little or no real site input. Opinions

may be sought, but too little notice taken of them – resulting in recruitment delays, later protocol amendments and frustrated investigators. Some companies are now willing to invest in feasibility work spending a small amount of money up front to pre-identify patients in the 'real world', seeing if the protocol is viable in clinical practice, and in which countries/regions / hospitals the patients are likely to be found. This requires a deep understanding of regional/site variability in clinical practice. Hopefully once formed this will become a hard habit to break! This information enables companies to write recruitment plans including approaches to meetings, advertising, risk management and contingency plans. Investment in protocol feasibility and market research, in advance, will lead to more clearly defined recruitment strategies as critical components of the overall clinical development plan.

> *"The term 'feasibility' can apply to a range of activities, the level of accuracy relates to the time and effort invested"*
>
> *Linda Carruthers, Director of Clinical Operations, Profiad Ltd*

Getting to know investigators better e.g. investigator focus meetings – designed to understand what investigators want from the trial process and how companies can improve relationships generally with sites to better understand site capabilities and expectations.

This approach is likely to yield results – but may be expensive to deliver. It requires detailed understanding and segmentation of the investigator population in terms of the value delivered to the Pharmaceutical sponsor, if it is to return the investment made. In order to do this, Pharmaceutical companies also need to improve the capture and retention of basic factual information on sites including performance metrics; how many patients were screened per patient entered, how many queries per patient, drop out rate etc, and also more basic information about the site: capabilities, staff, addresses, contact numbers and so on.

Accessing investigators through CROs and SMOs – using these organisations to take advantage of their more sustained relationships with sites.

In the year 2000, CROs played a significant role in 65% of all drug trials (or 52,000 trials). Their ability to positively (or negatively) impact investigator experiences and performance during the trial is enormous; but how well is information about those experiences captured and re-used when the site is next approached? SMOs on the other hand, clearly know their sites well, providing a positive argument towards the benefit of SMOs that own their own centres and yet this is not "failsafe". This route will become increasingly beneficial if CROs and SMOs succeed in developing closer ties with one another and stop competing when their service offerings are often complimentary.

Improved training and education of sites. Survey results show that approximately 52% of investigators only ever do one trial. Whilst the reasons for this are not clear, they are likely to include a failure to meet expectations on one or other side, and the fact that in effect the investigator is subsequently 'lost to follow-up' and remedial actions are never taken. Many companies are now beginning to consider the need to improve investigator training and education on the trials process in general, looking to e-learning opportunities as a possible tool to help with this. Ensuring that all investigators are fully briefed and have all the trial literature and study materials will assist patient recruitment. In the longer term it will be critical that all training and support materials are presented in a format that will appeal to the patients and not just the physicians.

> *"It is important to remember that in many countries and studies, retention of the patient is just as crucial as recruiting them in the first place"*
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> *Tom Ruane, Director, Investigative Services, Quintiles*

Recruitment on the internet

This can take the form of directly attracting patients or using the internet to increase awareness of trials in the investigator community. So far, the internet has not delivered the miracle solution some had hoped for, and nor is it likely to unless it is used as part of an integrated approach. The internet has yet to achieve the levels of success that have been witnessed from more traditional sources, such as local media, via newspapers, magazines, radio and television advertising. Ultimately the internet may replace these, but for the foreseeable future they will be used in conjunction with one another. However, if considered part of the recruitment toolkit, the internet has huge benefits in enabling companies to post trials where patients and investigators can find out about them. In fact the FDA now want Pharmaceutical companies to list all their trials for critical/life-threatening illnesses on websites (FDAMA 113) – but the challenge lies in how those investigators and patients are managed once they try and contact the company. Some companies have set themselves up to act as 'information brokers' in this, helping to match appropriate investigators (or patients) and trials e.g. ClinicalTrialFinder.com. A recent survey by Datamonitor found that 92% of surveyed US physicians and 80% in Europe are either currently using the internet or are interested in doing so for finding information about clinical trials for their patients. What is clear, however, is these contacts need proactive, co-ordinated management to deliver value to the sponsor organisation.

The internet will be used increasingly to screen and potentially contribute to simple pre-selection of patients, as long as it is simple and highly user friendly. Touch screens situated in convenient, accessible and highly visible locations will maximise the impact. Providing potential patients with increased and timely feedback will help, as will the likely positive impact if patients are convinced of the safety and efficacy of the studies, along with the security and confidentiality of any data presented.

In summary Pharmaceutical companies have many options to improve patient recruitment. Ultimately much more of this recruitment may take place directly with patients – but in the meantime the investigator remains key in the decision to participate and to remain in the trial. A recent Harris poll, investigating the impact of the investigator on a patient's likelihood to participate in a trial, shows very clearly that the amount of effort made by the investigator to encourage patient participation corresponds well with the likelihood of patient participation. Therefore, learning to work more effectively with the investigator community will be a critical success factor for the clinical trial process for the foreseeable future. This, together with increasing use of EDC has implications for the roles of CRAs – freeing them up from day to day box checking, and requiring them to become

excellent coaches, mentors and relationship managers in the sites they manage for the clinical trials process. In the IBM Business Consulting Services Pharma 2010 publication they envisage many routine interactions in the trials being handled through contract / co-ordination centres staffed in part by medically qualified and experienced trial personnel. Pharmaceutical, Biotechnology and CROs need to review and evaluate their CRAs in this changing environment and in doing so how many will prove able to face the challenge of this exciting new role as an 'account manager' of one of the industry's key strategic assets – the investigator?

"There is a growing understanding that successful CROs capitalise on the benefits that SMOs offer. CROs focus on their areas of expertise rather than true site management"

Linda Carruthers, Director of Clinical Operations, Profiad

Patients need to be recruited in the markets where products are ultimately going to be marketed. Companies will have to take a more proactive approach and be prepared to invest both the time to educate and the financial resources to attract. They must listen more closely to the investigators opinions, advice and needs. Industry must accept that the investigators have the greatest understanding, and more critically, influence over their own patients. All the evidence indicates that whilst very few patients that are eligible for involvement in clinical trials do so, a significant proportion have indicated a willingness to do so. The interest is there, but somehow these "window shoppers" must be converted to "buyers". The potential solution will require sponsors, either directly or via CROs and SMOs, to invest significantly more in understanding their customers, and critically to have these relationships managed sensitively and intelligently via their CRAs or study site co-ordinators as they rapidly evolve into key account managers who take responsibility for these critical and highly sensitive relationships.

"The clinical trial patient in 2003 is much more questioning, sophisticated, demanding, and in some instances more litigious than they have been previously"

Tom Ruane, Director, Investigative Services, Quintiles

In order to ultimately overcome the multifaceted problems with patient recruitment there must be an acceptance of the need to:

- Identify and invest in the appropriate patient population
- Gain the trust of the patient population
- Accept the need to rapidly drive change in the responsibilities, attributes and competencies of CRAs in 2003
- Understand the expectations and needs of investigators
- Investigate further into geographical and patient feasibility
- Allow investigators and/or the sites to have greater influence in trial design
- Invest significantly in pre-trial marketing
- Genuinely partner and share with their CRO and SMO providers
- Track investigators smartly to understand what makes a "good" investigator
- Explore openly all avenues for increased recruitment utilising new technology alongside proven methodologies
- Manage their data more efficiently
- Share information and experiences with competitors

It is critical that sponsors accept that the world of clinical trials and patient recruitment is changing rapidly and irreversibly. Companies must acknowledge that their traditional competitors could and should become allies. By sharing experiences and data, which to date they have been inefficient in collating let alone interpreting, it will be possible to not only draw more meaningful conclusions, but to reduce the time and investment required. Increased communication between all parties will make a significant impact immediately, assuming that communication occurs in all directions, genuinely involved in the imparting or exchanging of information and ideas and that all parties recognise the importance of listening!

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