Accelerating patient recruitment

Advice on how to tackle one of the industry's major problems.

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The annual cost of clinical trials in the US is $7 billion; the estimated cost of patient recruitment is $1.89 billion. These costs are subject to further increases with each day's delay in bringing the product to market. Industry sources claim that for every day lost in development, it costs $1 million in lost sales. A recent article claimed that only 15% of clinical trials are completed on time, with over 50% of delays attributed to patient recruitment and 30% of investigator sites failing to recruit a single patient.

Contributing to the mounting pressure for effective patient recruitment is the rising demands of regulatory bodies for an increase in the number of trials per NDA filed and a rise in the number of patients required per trial. The average regulatory submission contains data on over 4,000 patients; however, the time available to recruit these patients has gone down as the industry has to maximise its ROI by reducing the time it takes to complete product development programmes.

The situation is further complicated by a combination of factors that have resulted in the general public – and hence the pool of potential trial participants – being wary of the medical profession and pharma industry and subsequently reluctant to 'sign up' for clinical trials. In many countries, the industry has a less than perfect reputation, deserved or not, and more patients are increasingly unwilling to take part in company sponsored clinical trials when media scares about drug safety or 'dirty' dealings of clinicians being 'paid' to take part in clinical trials are an almost daily occurrence. The release of vast quantities of information onto the Internet, much of it inaccurate, confusing and offering conflicting advice, has not helped the industry in its courtship of prospective trial participants.

In addition, the industry's success in the development of effective medicines has provided both patients and doctors with a wider range of satisfactory treatment options. This has reduced the incentive to take on any perceived additional risks of side-effects or lack of efficacy by participating in a clinical trial.

The efficiency of the recruitment process is hampered further still by competition for a limited number of clinicians and investigator sites in specific therapeutic areas, resulting in sponsors targeting a limited pool of patients for their clinical trial. The emergence of site management organisations (SMOs) and investigator networks has also contributed to the potential delays in patient recruitment with preferred supplier agreements resulting in restrictive access to investigators. The problem has been magnified by the traditional approach in the past of not giving due prominence to the development and execution of patient recruitment strategies as an integral part of the study process. Sponsors and CROs have recognised this fact and the situation is improving; however, it is estimated that only 5% of patients with a particular disease indication ever come forward to participate in clinical trials.

The question, therefore, is how to address the factors (summarised in **Fig 1**) that are resulting in the increased competition for patients and the need for accelerating their recruitment. In addition, rather than competing for the current pool of patients, the industry needs to consider how to increase the size of the patient pool and find access to the 95% of patients that do not currently come forward to participate in trials.

Developing an effective recruitment strategy

Firstly, adopt a philosophy and approach to patient recruitment that ensures the process is an integral part of the clinical development programme. Develop a planning framework that has a number of key components against which one can leverage activities that allow recruitment policies to be implemented to meet the needs of the clinical development programme.

A clinical trial starts with developing the protocol. It can be argued that the difference between good and poor patient recruitment starts at this point. Often, it is all too easy to construct a protocol that is perfect in terms of scientific design, but the question always in the background should be, 'How feasible will this be to implement in the field?' For example, we have noticed an increasing tendency towards over-restrictive inclusion/exclusion criteria in trial protocols. There is an understandable desire to maximise treatment differences and avoid analytical bias through 'clean' protocols. However, the clinical reality is full of 'greys' and a naturalistic approach is also important. In a trial we recently conducted, the protocol specified a laboratory parameter in the inclusion criteria for which there was little background information in the patient population.

Realistic expectations

With a well thought out protocol in hand, the next consideration for the success of your recruitment strategy is setting realistic expectations. It is important to get a good sense of the incidence and/or prevalence of the disease in question. This may vary from one geographical area to another; even within a single country there may be local differences. One can estimate the effect of the protocol criteria on reducing the total patient population based on the performance of similar trials in the past and by entering into an effective dialogue with investigators. You need to consider what variations may occur in patient populations due to cultural or ethnic differences and the spread of individual sites in relation to patient populations, as well as the internal healthcare facilities in different countries and the impact this has on the site's ability to recruit patients and conduct the trial.

The impact of local regulatory policies should also influence the decision on which sites to work with. This should be supplemented with an audit of sites, patient records or registries, previous experience and any historical recruitment metrics they have for similar trials to aid the process of identifying what sites can meet your recruitment needs. Analysis of medical journals, databases and published papers from conferences and meetings can help identify potential investigators, rising stars and active opinion leaders – however, one should also consider the experience of their study site staff as these are the individuals who often carry out the work load of the study.

We find that too often sites overestimate the number of patients they can recruit because they are often not initially familiar with the protocol and the effect its selection criteria will have on the total patient population. We therefore suggest a protocol synopsis and one-to-one discussions between sites and an experienced clinical researcher are required in order to estimate realistic numbers and secure agreements on the expected performance of individual sites. In addition, we strongly advise the use of competitive enrolment together with the inclusion of back-up sites so they can be brought on board should individual sites drop below their agreed target levels. This is sometimes perceived as causing potential difficulties for a company wishing to work with that site in the future; however, our experience is that it works well so long as expectations are made clear at the beginning. It is also important to ensure that regular communication with sites and investigators is encouraged and maintained; this can facilitate the early identification of recruitment problems and help to develop a communication channel that can be utilised to help deal with such problems.

- Greater patient exposure to the drug for regulatory submission
- Patient and clinician satisfaction with current therapies
- Competitors with trials in the same disease indication
- Tying up investigational sites by CROs/SMOs
- Poor planning or lack of specific recruitment policies
- Lack of patients coming forward for or aware of clinical trials

Fig 1. Factors causing increased competition for patients

Leveraging the opportunities for success

Having selected your pool of investigators, make the investment in terms of time and money to ensure they are fully briefed with trial literature and study materials that are user friendly to both investigator and patient. Consider the use of educational material for both patients and site staff; this will aid recruitment by offering reassurance and information to all participants in the study. Make sure that they have a clear understanding of the study protocol and that they have bought into what is expected of them. The format and timing of your investigator meeting should be designed to both inform and motivate and help provide an early impetus for patient screening and the entry of patients into the trial.

The timing of the meeting should form part of an integrated range of activities designed to maximise the opportunity for patient recruitment and communication with the widest patient population. Consideration should be given to the utilisation of the following activities based on the needs of the individual trial:

- Promotion via patient organisations, newsletters and websites
- Advertising in local media (press, TV, radio, poster sites). This will be subject to ethics committee approval, but all materials should be designed and approved in advance so they

can be used in the recruitment activities
- Production of posters, flyers and leaflets for surgeries, local clubs/institutions and locations that match the patient profile
- The use of appropriate Internet portals and websites promoting and providing information on clinical trials currently being undertaken and the opportunity for patient enrolment, such as www.centerwatch.com. This can be used to both boost recruitment and provide details of investigators to potential patients
- The launch of a dedicated website for the therapeutic area or promotion on appropriate consumer healthcare sites, supported by information about these sites within all your other promotional activities
- An educational campaign targeting the public and communicating the need and nature of clinical trials and calling for patients to participate and help in the development of successful medicines
- The placing of articles in targeted newspapers or magazines written by well-known clinicians or a relevant celebrity, linked to a website or free phone call centre
- The use of research centres and SMOs – by using these facilities one can boost recruitment by opening out the study to a larger number of patients with whom they already have contact, and take advantage of local knowledge, which can be vital if conducting a trial on a global basis.

For the first seven options, in order to aid the recruitment process, information directing the patient to a call centre or website for pre-screening could be part of the process and hence facilitate the speed and accuracy of recruitment.

An important element to the success of a study's recruitment strategy is regular and optimal access to information about what is happening at individual sites. This is especially true with regard to the management of global trials where day-to-day contact may not be practical and the time delay between monitor visits can impact on the identification and solution of problems that could have a dramatic impact on patient recruitment.

Consideration should therefore be given to the use of electronic clinical trial management systems that allow real-time access to study data and the performance metrics of individual sites. Some systems offer the use of secure websites as an integral part of their system for communicating with sites. These can vary in their functionality and can be developed to meet the need of individual studies. On a daily basis, clinical research personnel at both the sponsor company and the CRO can gain access to this information and be in a position to:

- Have daily access and regular communication with investigator sites
- Monitor on a daily basis the number of patients recruited, their eligibility, screen failures and to obtain feedback that will allow them to identify trends and demographic variations in the recruitment process
- Rapidly identify and manage poorly recruiting investigator sites, thereby providing the opportunity to cut out poor performers early in the programme and bringing on board back up sites
- Identify and respond rapidly to the needs of individual sites and hence adapt and refine the recruitment programme to meet their needs.

- Realistic protocol design
- Detailed estimates of likely patient population
- Clear sponsor-site expectations
- Production of support/educational study materials for investigators and patients
- An integrated media and advertising approach
- Use of PR opportunities
- Partnership with patient organisations
- Appropriate use of specific Internet sites
- Adoption of new technology
- Real-time access to study information
- Use of experienced clinical project management team
- Better understanding of the nature and need for clinical trials
- Meeting the information and practical needs of the patient

Fig 2. Options for enhanced patient recruitment

Daily access to this information provides sponsors with the opportunity to identify what activities need to be leveraged or modified to ensure sites meet their recruitment targets and improves the speed and efficiency of the clinical trial process.

The use of the Internet for the management of clinical trials and recruitment of patients has increased dramatically over the past five years. Specialist companies offer a variety of 'pay for' services designed to facilitate patients and investigator access to enrolment in clinical trials. This approach has offered the opportunity for communicating with a wider patient population and has the potential to increase the size of the patient pool. The Internet can be utilised in a variety of ways; however, the following points should be considered:

- The use of on-screen, screening questionnaires that are user friendly to ensure patients are sufficiently eligible for pre-screening telephone contact
- Provision of instant feedback to potential trial participants with a methodology to guide them to the relevant participating site with the understanding that there may be limitations on enrolment due to the distance between the site and potential participant
- Potential selection bias due to the demographics of Internet users – how close does this fit your patient profile?
- The variation on the use of the Internet in different countries and the stance of different ethics committees on its use for recruitment
- The need for security and confidentiality of patient data.

The Internet should be considered as a potential weapon in the industry's armoury of tools for accelerating patient recruitment, its utilisation based clearly on defined objectives and on evidence that it can be shown to have a positive impact on patient recruitment.

The options that should be considered in the development of a study's patient recruitment strategy are summarised in **Fig 2**. The activities used as a consequence of the strategy adopted should form part of an integrated approach that will accelerate patient recruitment and provide the opportunity to increase the size of the patient pool available for participation in the clinical trial. This integrated approach will lead to an increase in the efficiency, precision and speed of clinical trials, reducing the time required for clinical evaluation and bringing the product to market faster.

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