Accelerating Patient Recruitment with an Integrated Approach

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There is a persistent and growing problem of finding sufficient patients who are willing and able to participate in clinical trials in Western countries. This has led the pharma industry to cast the net wider and there are now plenty of examples of large pivotal trials being conducted in Central and Eastern Europe, Latin America and the Far East. However, despite the attractiveness of drug naïve patients, there are many problems inherent in conducting trials in these countries, not least a lingering suspicion at some regulatory agencies over the quality and integrity of data.

Over the past few decades, a great deal of time and money has been invested in raising the quality of clinical trials in Western investigational sites. Ideally, the industry can continue to recruit most patients from these traditional sites, but to do so requires a more thoughtful approach to patient recruitment. In this article, I will suggest ways of accelerating patient recruitment.

COMPETITION FOR PATIENTS

There are several factors increasing competition for patients, as illustrated in Table 1 opposite. A major aspect is the growing number of patients exposed to the investigational drug required for regulatory submission. The need to define safety in a reasonably sized population has led to the average regulatory submission containing data on over 4,000 patients. Moreover, the industry's success has caused problems. In many disease indications there are very good treatments available, which lead both the patient and their doctor to ask why they should bother taking part in a trial of a new investigational drug with the risk of side effects or a lack of comparable efficacy. Some therapeutic indications are subject to intense competition from different sponsors who are chasing a finite patient population for their clinical trial. We have seen companies attempt to 'own' investigational sites through promises of work volume and investment in research infrastructure at the site – indeed, many SMOs adopt this as a fundamental principle of their business and service offering.

However, with up to one in four clinical trials experiencing significant delays, adding months – if not years – to the development cycle, there needs to be a rethink. Instead of competing for the current pool of patients, why not increase the pool?

It is estimated that only five per cent of patients with a particular disease indication ever come forward to participate in clinical trials. The question is therefore how to access and encourage the other 95 per cent – either directly or via their doctor – a classic situation that is amenable to methods of modern communication.

BUILDING THE RECRUITMENT PYRAMID

A clinical trial starts with developing the protocol. It can be argued that the difference between good and poor patient recruitment also

Table 1: Factors Causing Increased Competition for Patients	
◆ Greater patient exposure to the drug for regulatory submission	◆ Tying up investigational sites by CROs/SMOs
◆ Patient and clinician satisfaction with current therapies	◆ Poor planning or lack of specific recruitment policies
◆ Competitors with trials in the same disease indication	◆ Lack of patients coming forward for clinical trials
	◆ Lack of patients who are aware of clinical trials

begins at this stage. Often, it is all too easy to construct a perfect scientific design. However, the underlying question should always be: 'How feasible is it to implement this in the field?'. As a practising physician, I 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 grey areas, and a more naturalistic approach is also important. In a recently conducted trial, the protocol specified a laboratory parameter in the inclusion criteria for which there was little background information in the patient population. After screening over 80 patients, none were eligible, based upon this parameter requiring much discussion and a protocol amendment. In reality, the parameter contributed little to the science but prevented recruitment by excluding almost all the patient population.

With a well thought-out protocol in hand, the second part of the pyramid 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 regional differences. One can estimate the effect of the protocol criteria by reducing the total patient population based on past experience, performance of similar trials in the past, and by speaking to investigators. The latter is sometimes no more than a cursory discussion, which can lead to problems. In my experience, sites over-estimate the number of patients they can recruit, not because of inaccuracy, but because they are often unfamiliar with the protocol and the effect that its selection criteria will have on the total patient population. As such, a protocol synopsis and one-to-one discussions with an experienced clinical researcher are necessary in order to estimate realistic numbers. At this stage, I consider it important to agree with the site on their expected performance. Competitive enrolment is more or less *de rigueur* nowadays, and we expect sites to drop out of the study to allow back-up sites on board, should performance significantly drop below that previously agreed. I know that this is sometimes perceived as causing potential difficulties for a company wishing to work with that site in the future; however, my experience is that it works very well so long as expectations are made clear at the outset – indeed, one can sometimes sense the relief at the under-performing site when asked to discontinue their involvement.

The first few days and weeks of the study are the most critical to recruitment performance. At this time, motivation and enthusiasm are at their highest, the site personnel have recently undergone familiarity training and the relationship between the sponsor and the site personnel is at its best following the investigator meeting in an exotic location. This is the point at which excellent recruitment performance is set, and every appropriate lever must be pulled to achieve momentum in screening and introducing patients to the trial. This is also when communicating with the widest patient population can produce results. Good patient recruitment can be achieved in several ways, as outlined in Table 2 below.

Good sites will have already examined their past records or patient registries, and may even have invited suitable patients to the screening visit or pre-screened them by telephone. It is worthwhile ensuring that the site does examine its records as this process sometimes gets missed – disease incidence based on memory is not always verified by a trawl through the patient database. Advertising in the local media can draw in vast

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Table 2: Options for Enhanced Patient Recruitment	
◆ Realistic protocol design	◆ Patient organisations
◆ Detailed estimates of likely patient population	◆ Specific Internet sites
◆ Clear sponsor site expectations	◆ Real-time access to study information
◆ Media advertising	◆ Better understanding of the nature and need for clinical trials

numbers of patients. This can take the form of posters in doctors' surgeries, in local clubs and institutions, flyers on the sides of buses or in railway stations, or advertising on the local radio. However, in most countries, advertisements need to be approved by an ethics committee, which can lead to rather bland messages. This often results in many enquiries from patients who are clearly ineligible to take part. One way around this is to direct the patient to a call centre or another central point where pre-screening by telephone can take place.

In some therapeutic areas, editorial space in specific newsletters or magazines can be useful. Many chronic diseases such as arthritis, dementia, depression and HIV have patient advocate organisations that publish their own in-house materials. An article written by a well-known clinician can be informative and can contain a link to a website or a freephone telephone number.

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The advent of electronic clinical trial systems that allow real-time access to study data is an important factor in bringing together all the recruitment options. On a daily basis, clinical research personnel can monitor the number of patients being recruited, their eligibility, screen failures and a host of demographics. Individual site performance can be tracked in a sensitive manner and changes can rapidly be made in response to poor performance or, even better, trends which reveal the likelihood of problems occurring.

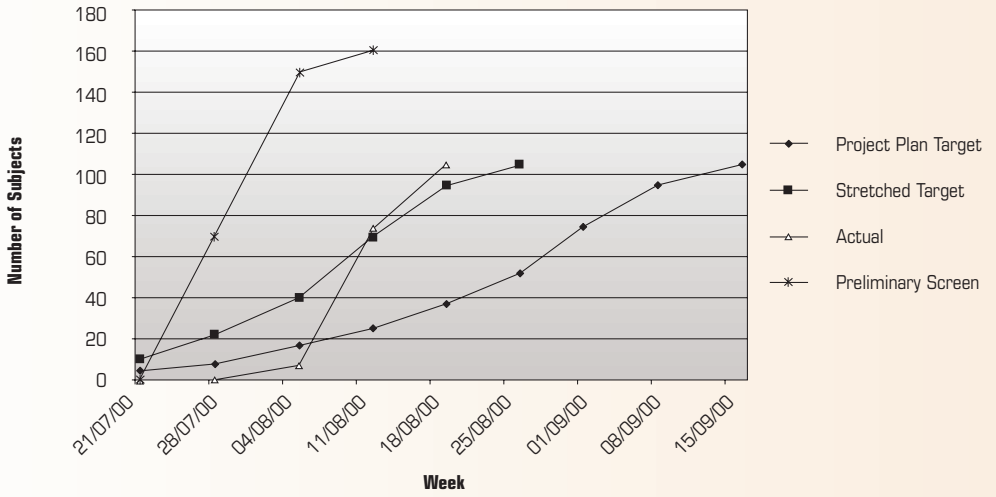
RECRUITMENT VIA THE INTERNET

The Internet is currently attracting a lot of attention as a means of enhancing patient recruitment. There is no doubt about its usefulness as a mass communication medium. It is estimated that 15 to 20 per cent of Internet use is by people seeking information on health, well-being, diseases and treatment. Sites such as CenterWatch carry details of clinical trials placed by sponsors and the site boasts many thousands of hits each day. Patient organisations such as the Alzheimer Research Forum contain information about clinical trials in specific disease areas. Pharma companies such as GlaxoSmithKline are exploring the use of their own websites containing information about their clinical trials.

However, despite some of the hype generated by companies offering patient recruitment across the web, this is no magic bullet, and like most things with the Internet it needs careful integration into the overall clinical trial recruitment process. Experience of using the Internet has shown that large numbers of potential patient contacts can be generated. However, there is the same disadvantage here as with other forms of advertising, in that many are ineligible for the trial. The problem is compounded by the fact that there is no focus on geographical locality and there is little point in generating a contact from a patient who is hundreds of miles from the investigational site. Fortunately, the Internet enables much smarter ways of screening patients before a contact is generated. Screening questionnaires can be placed on the site, which, provided they are well-crafted and user-friendly, get the patient to do the work of ensuring that they are at least sufficiently eligible for a pre-screening telephone contact. The best questionnaires will give instant feedback to the patient as they fill in their responses and may even direct a patient from one clinical trial for which they are not eligible, to another for which they are. The advantage of these sites is the level of control they give to the patient. As human beings, we all find it easier to interact with the computer screen when we are a little unsure of whether to commit, rather than the more pressurised situation of a one-to-one telephone discussion.

However, several disadvantages have been highlighted, including the potential for selection bias. The profile of the typical Internet user seeking health information is usually well-educated, middle class, female and aged between 35 and 55 years. Such people may have different prognostic factors from the wider population, though this should only come into play if all recruitment came through a website, which is unlikely. Use of the Internet varies from country

Figure 1: Proof of Concept Study – Recruitment Metrics



to country, with the US having the most successful experiences so far. Ethics committees in most European countries are yet to decide their policy on using the Internet for patient recruitment, though the past attitude of resistance is softening. Part of the problem lies in the confidentiality of patient data. Irrespective of whether the initial contact is anonymous, at some point the patient's name and medical history must be disclosed, and there are concerns that this information has a commercial value to third parties.

In our experience, the Internet is useful for generating enquiries from patients but is not a replacement for proper screening with a health professional who is familiar with the study. For us, it is an ideal medium through which to communicate with the wider patient population, thus increasing the patient pool.

All stops must be pulled out in order to gain accelerated patient recruitment. In a trial conducted in Summer 2000, the patient population and selected investigational sites able to access patient registries in general practice were carefully targeted. A high level of media advertising was undertaken in the towns and cities surrounding the investigational sites. They were constantly encouraged to spend more than the usual time and effort on recruitment at the beginning of the study. The results are shown in Figure 1 above. There was a high throughput of patients to screening which, as a result of telephone pre-screening, ensured maximum effort was invested in getting a high proportion of eligible patients to the screening visit, in turn ensuring randomisation. Overall, recruitment was complete in half the time our client had predicted in the project plan, and there were only two screen failures.

INFORMING PATIENTS

If so many patients are not participating in clinical trials, perhaps we should ask why? A perception remains that the pharma industry is, in some way, exploiting patients in clinical trials. We still have a long way to go in shaping a sense of true partnership with the general public in the development of new medicines. There is a good deal of old-fashioned altruism out there, but we live in an age where anecdotes in the general media are more powerful mediators of public opinion than well-documented scientific fact. In the past, the industry has adopted an approach of quiet, systematic explanation, but this tactic is drowned out by the latest scare story which is usually based on barely founded truth. Perhaps the greatest contribution of the Internet to patient recruitment will be the dissemination of factual, unbiased information on the nature of and the need for clinical trials for new medicines.

CONCLUSION

Despite the difficulties many companies face in recruiting patients to clinical trials, only a fraction of the patient population actually participates. The beginning of a trial is the time to pull out all the stops and implement an integrated recruitment plan. This may involve patient registries, media advertising and the Internet. Most important of all is to ensure that protocol requirements reflect real patient profiles and to ensure clarity of expectation between the sponsor and the investigational sites. If done well, an integrated approach to patient recruitment can significantly accelerate clinical trials. ◆

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