



Patient recruitment for clinical trials

Encouraging positive outcomes

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In association with Chiltern International



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About Chiltern International

Established in the UK in 1982, Chiltern has accumulated vast experience running clinical trials across a broad therapeutic range (phase I to phase IV) with a wide variety of clients. With offices throughout the United States, Europe and Asia, Chiltern can provide an extensive range of services for both international and national projects.

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Patient Recruitment

Drug development

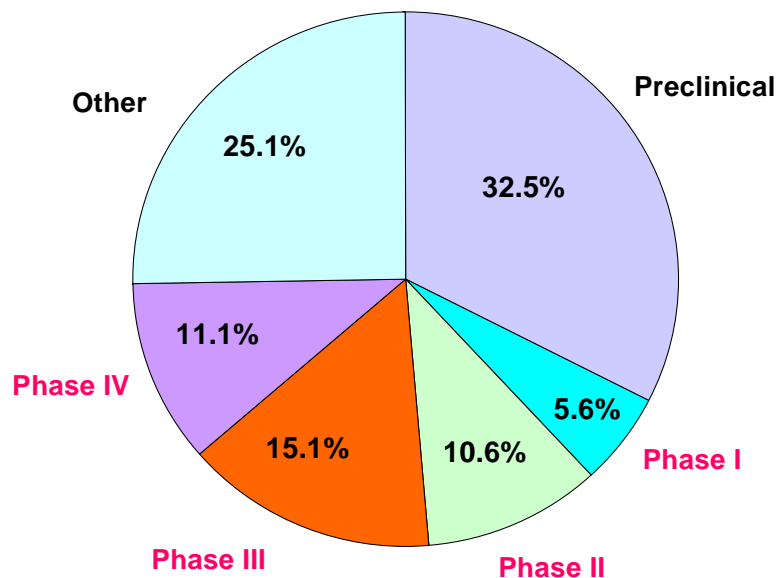
The pharmaceutical industry is one of the most R&D-intense technology-based sectors and has been consistently increasing its investment in research. As an industry it is generally regarded as being more R&D-intensive than others (such as electronics, communications, and aerospace) in the technology sector (1). This commitment to research is illustrated by the fact that between 1990 and 2000, global pharmaceutical R&D expenditure increased by 121% (2).

The route to successfully launching a new drug is difficult. Only about 15% of new drugs entering development subsequently reach the market (3), and the overall expense can be in the order of US\$897 million (4). Furthermore, as drug development times lie between the 10- and 12-year range, R&D decision-making is crucial in order to best gauge how to expedite the process and ensure that the right product is brought to market. The field of drug development is fiercely competitive and patient and clinician acceptance of the final product is essential for success.

Rising clinical expense

Clinical development is a major part of the drug development process, and is the stage at which a compound exhibits its potential as a therapy for the general population. In 2000, the global pharmaceutical industry was estimated to have spent US\$58 billion on R&D, with around 40% of this being devoted to clinical trials (1).

Figure 1: US Domestic R&D Expenditure by Function



Not surprisingly, companies pay particular attention to the allocation of time, money and resources in order to manage the clinical trials that form their overall clinical development programme. In 2000, CMR International estimated that development projects consumed up to 10 times the resources consumed by a discovery research project (1). Thus project selection and prioritisation, before entry into the development process is an important decision point.

A number of studies have shown that the expense of clinical development is rising rapidly in relation to the other parts of the R&D process. This trend has prompted pharmaceutical and biotech companies to identify and reassess all the factors that play a role in clinical trials in order to maximize their investment and improve the process. The Tufts Center for the Study of Drug Development found that whilst total average (preclinical plus clinical) costs increased 5.8 times between the 1970s and 1990s, the corresponding clinical costs increased 8.6 times (4).

Companies involved in novel drug development frequently experience a heavy increase in expenditure when their compounds reach clinical trials. In its 2002 survey of its US-based member companies, the Pharmaceutical Research and Manufacturers of America (PhRMA) noted that the inflation-adjusted increases in clinical R&D costs were more than five times greater than the costs for preclinical work (1). Similarly, the Japanese pharmaceutical industry has steadily increased its clinical research activities. As a proportion of total Japanese R&D expenditure, clinical development costs rose from around 34% in 1998 to nearly 39% in 2000 (5).

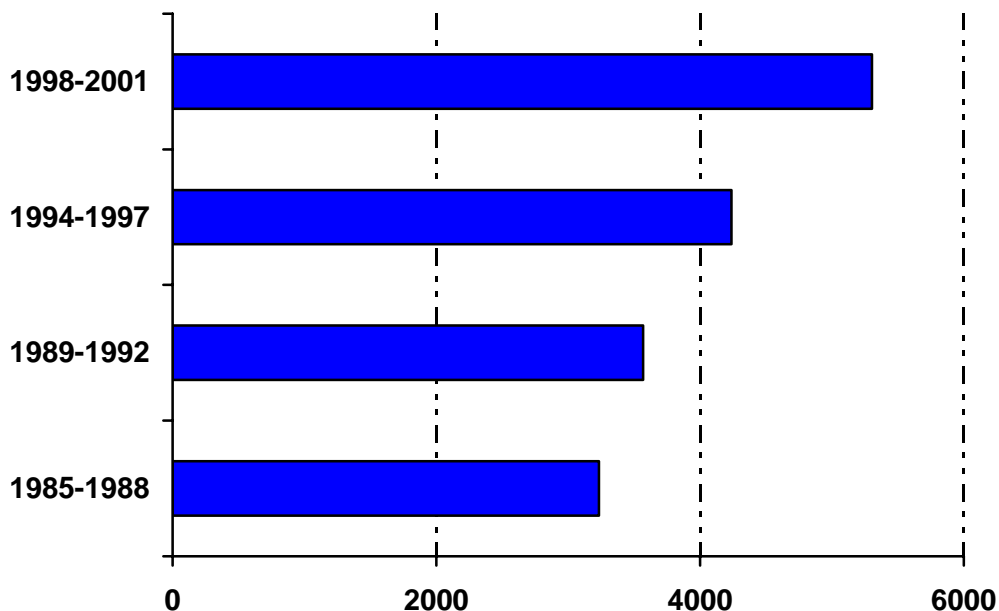
Patient recruitment matters

Although companies have brought in numerous technology and management measures to improve their clinical trials, inefficiencies in the process continue to present problems. One estimate suggested that despite technological advances in pharmaceutical R&D, nearly 80% of all clinical studies for new products failed to finish on time, and 20% of those were delayed for 6 months or more (6).

Efficient patient recruitment has been identified as one of the major factors for success in clinical trials. Large numbers of subjects are needed to generate high quality data that will convince regulators and clinicians, as well as future users in the general population, that a product is of clinical benefit. Companies are constantly under pressure to run additional trials to prove their claims about a particular product.

An analysis by CMR International, of 23 clinical dossiers submitted between February 1995 and April 1999 to regulatory authorities in Europe, the USA and Japan, found that the dossiers contained on average 35 clinical trials, involving on average more than 4,000 subjects each (2, 7). Another analysis estimated the mean number of patients per New Drug Application (NDA) to be 3,233 between 1985 and 1988 but for the period 1998 to 2001 this mean number had risen to 5,303 patients per NDA (8).

Figure 2: Mean evaluable patients per NDA



Source: Peck, C., “Drug Development: Improving the Process”; cited by: M-J. Lamberti. The Changing Climate of Clinical Research. Presentation at the Association for Clinical Data Management (ACDM) Meeting (15-17 February 2004 Bristol, UK).

As trials become larger and more international, the actual process of finding, screening, and recruiting clinical trial patients at multiple research sites is a challenge for even the largest pharmaceutical companies. Many organisations in the industry that specialise in recruitment solutions cite figures from CenterWatch suggesting that subject recruitment can take 25% of the timeline for the setting up and completion of a typical clinical trial (9, 10). Other sources cited suggest that 45% of all delays in clinical trials are due to subject recruitment performance, with most delays exceeding 6 months (9).

Companies frequently use external partners to help them manage their clinical trials, such as clinical research organisations (CROs) and experience in the field of international patient recruitment is highly valued.

Patient recruitment strategy

A degree of realism is required in order to optimise subject recruitment for clinical trials. Although there is always a time and cost pressure, any difficulties for a clinical project could actually be exacerbated if subject recruitment rates are approached in an unrealistic manner. Although there may be a potentially large number of subjects in the research area of interest, ensuring that subjects are enrolled for a trial in an ethical manner that meets all the appropriate local and international regulations is never straightforward. When looking at potential locations for trials, investigator selection, cultural issues and social factors may all play a role in subject recruitment. It is vital that companies are seen to recruit in an ethically sound manner and that all subjects fully understand their participation. The enthusiasm of investigators and subjects can be of immense benefit to a study.

When conducting patient studies, it is important to be as proactive as possible to identify sites that will be efficient at recruiting. Specialist recruitment plans and trial commitment fees can be very useful in this regard. With specialised recruitment plans, each centre is required to complete and sign documents, which state from where they will find patients for the proposed study and in what timelines this will be achieved. The advantage of this approach is that it gives something in writing from the centre and thus makes them more accountable. However, it also acts as a motivating factor for a centre to actively think about recruitment strategies from early on in the study, i.e. where their patients will be found and how the process of enrolment will take place. Competing trials can cause numerous problems, particularly for patient recruitment, but through having a proactive approach contingency plans can be devised to deal with such situations.

Figure 3: Outline of a typical recruitment plan

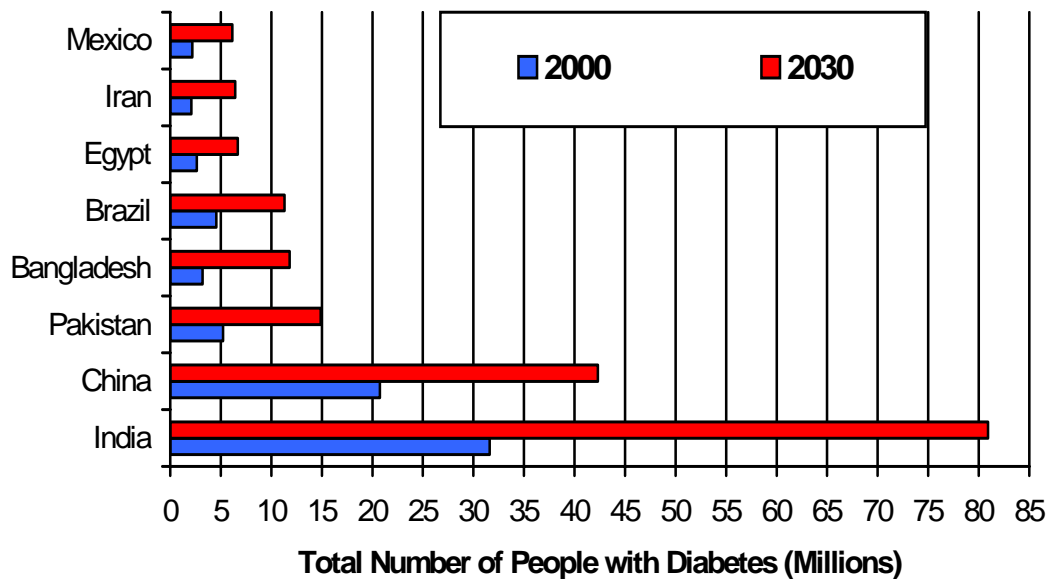
What is the source of the patients?
What number of patients will the site need to assess for suitability to meet the recruitment target?
What number of patients should discuss participation with a healthcare professional to meet the recruitment target?
Does the site have recruitment staff?
Is the recruitment schedule realistic?
Will the site sign the recruitment plan?

Global recruitment

As clinical trials have become larger they have also become more global. The internationalisation of clinical research is also important for companies in order to give local physicians experience of working with a new product. Companies often find that they need to run studies in more than one global region in order to enrol the required number of subjects. In particular, the presence of competing trials in a region can make the task of patient enrolment much more difficult and means that companies have to look elsewhere for eligible patients.

The past decade has seen emerging pharmaceutical regions such as Central and Eastern Europe, Latin America and South-East Asia increase in popularity as centres for clinical trials. The regions have large populations and the diseases that wish to be studied may be present in sufficient numbers for trials. Although these regions offer potential in terms of clinical development, it is important to make sure that trials are run to agreed international standards so that patients are protected and well cared for and so that the data generated in these regions is acceptable to the major regulatory agencies elsewhere in the world. There is an ongoing debate over the ethics of running clinical trials in developing countries.

Figure 4: Diabetes estimates and projections in selected developing countries



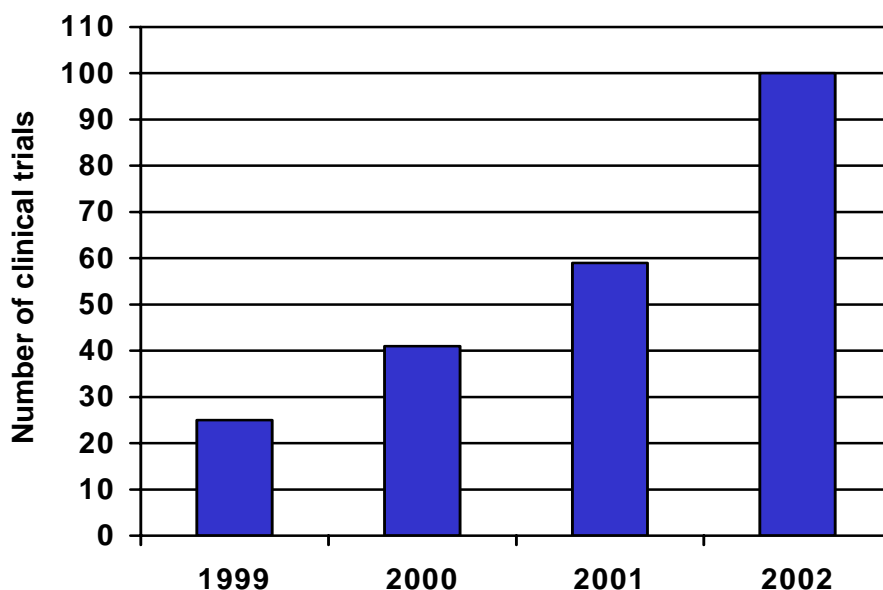
Source: World Health Organization

Although pharmaceutical companies may have operated on a commercial basis in emerging regions they may not have been actively involved in running clinical trials in these areas. This is where partnerships with specialised clinical research organisations (CROs) can prove advantageous. CROs operate globally and have first-hand experience of dealing with regional issues. A recent survey by Centerwatch of company outsourcing departments found that besides the USA and Europe, a number of respondents were managing outsourcing projects in emerging areas such as Latin America and the Asia-Pacific region (11). Certain respondents also indicated that they were handling outsourced projects in Africa and the Middle East (11).

As CROs work internationally across different therapeutic areas and on different types of products they often gain ideas on new approaches to important issues such as patient recruitment. This allows them to factor in local details into the international approach of the sponsor company. A good CRO will undertake appropriate feasibility to ensure that the particular global region can meet the desired objectives for the company in terms of clinical development. With clinical trials, although patient availability and recruitment will be evaluated, other issues will include study centre and investigator suitability, local regulations and of course resources, timelines and costs. The decision-makers must weigh up all such factors along with patient recruitment details before plans can be made to carry out a trial.

An example of this approach can be seen with respect to Central and Eastern Europe (CEE). At present, it is estimated that the number of multi-centre clinical trials being carried out in the CEE region is growing on average at an annual rate of 30% (12). A number of CROs have expanded into this region and have accumulated considerable experience in the various countries that make up the region. Their expertise has become increasingly valuable to companies wishing to run clinical trials here.

Figure 5: Clinical trials registered by Western companies in the Ukraine



Source: Chiltern International

The perception of high patient recruitment rates and cheaper costs associated with the CEE region have led to various companies attempting to develop their drugs in these countries. However, CEE is a very large area, comprising of many different countries with their own customs and systems, and it is important that the sponsor carefully selects which individual countries will best suit their needs (12). High patient enrolment rates should not be assumed in the absence of first-hand information on the centres being used and cheaper clinical development costs should not be automatically expected. In reality, companies should focus on achieving advantages in CEE in a cost-effective manner for their studies. In some cases, some upfront costs may be necessary in order to supply centres with specialist equipment that their US and European counterparts might take for granted. Although the cost of setting up complex studies in CEE may sometimes be higher than in other regions of the world, with the right strategy such costs should be offset by the benefits of rapid patient recruitment and rapid study approval (12).

It is likely that the global outsourcing focus of companies will continue and therefore knowledge of running clinical development projects in emerging regions will become a powerful reason for working with a particular external organisation such as a CRO.

The ethical angle

Everyone involved in clinical development has a duty to look after and care for patients involved in trials wherever they are and commercial objectives should not compromise this stance. In industrialised countries, the regulatory, ethical and clinical research environments are fairly well defined and so companies have sufficient previous experience to help them adapt to further changes in these regions. However, with emerging regions of the world these environments are less clear-cut and guidelines often ill-defined.

Companies are beginning to operate to an ever-greater extent in developing regions of the world and although they are focused on the commercial issues for their product, they must ensure that they are not seen as exploiting local populations in these areas (13–15). Although this is often stated by the pharmaceutical industry there are many observers who have called on the industry to demonstrate this very visibly so that can be no doubt (13).

In particular there has been considerable controversy over the issue of providing patients in these areas with the therapy after the trial has finished. Many of these developing regions will not be major markets for the drug if it successfully developed and as these patients are usually poor they will be unable to continue with the treatment once the trial has ended. Companies do

not tend to continue to offer the treatment in these developing regions once the trial is over, whereas in industrialised countries a system for the patient to continue receiving the drug is often offered. In the USA special programmes exist that help needy people to gain access to the drugs they require (13).

There are many who believe that the industry should move towards providing patients in developing regions with drugs after a trial has ended. As this would result in considerable expense for a company due to setting up distribution systems and training healthcare personnel to administer the drug this is not standard procedure (13). Many companies have tried to introduce a better system to deal with patients in these regions, but it is the lack of binding international guidelines in preventing patient exploitation in these regions that worries ethicists (13–15).

As clinical trials extend into developing global regions, it will be up to companies to ensure that they understand these issues when recruiting patients for their studies. Furthermore, they must treat potential investigators with the appropriate respect and must not be perceived as having a 'superior attitude' to those they work with in these regions. Public criticism of the pharmaceutical industry is at an all time high and so these issues must be confronted if companies wish patients to value their work and participate in clinical trials.

Encouraging patient participation

As a whole the pharmaceutical industry could be helped in terms of patient recruitment for trials if the public better understood the value of clinical trials and their role in the development of new medicines. It is imperative that adequate attention is paid to informed consent procedures so that potential patients understand their involvement in a clinical trial. If the public were more confident about being involved in clinical trials then more would participate.

For example, according to a US online study of nearly 6,000 cancer patients conducted by Harris Interactive in October 2000, most had never been told about the possibility of enrolling in a clinical trial for their treatment (16). The survey was supported by the Coalition of National Cancer Cooperative Groups, the Cancer Research Foundation of America, the Cancer Leadership Council, and the Oncology Nursing Society. Around 75% of the respondents stated that they would have been willing to enrol had they known it was a possibility, but 85% indicated were either unaware or unsure that participation in a clinical trial was an option (16).

Nevertheless, not everyone that considers enrolling in a trial will necessarily participate. Of those cancer patients who were aware of the clinical trial option, three out of four actually decided not to participate citing four primary reasons:

- they thought the medical treatment they would receive in a clinical trial would be less effective than standard care;
- they might get a placebo;
- they would be treated like a 'guinea pig'; and
- their insurance company would not cover costs.

Yet, the vast majority of those surveyed who participated in a clinical trial had a positive view of the experience. Ninety-seven per cent said they were treated with dignity and respect and rated the quality of care they received as 'excellent' or 'good'. More than 80% believed that they did not receive more tests than had felt were necessary and most (86%) said their treatment was covered by insurance (16). Interestingly, in June 2000, then President Clinton issued a Memorandum that allowed Medicare to pay for routine patient care costs associated with clinical trials (17).

In the general population another Harris Interactive online survey found that although 82% of the cancer-free people polled would consider enrolling in a clinical trial if faced with the disease, they shared some of the concerns of cancer patients who did not participate (16). Therefore there remains a gap to be bridged in terms of communicating with patients. Supporters of the survey suggested that patients should ask their doctor or nurse about potential trials and use the Internet for general information. Furthermore, if they found a trial of interest they should

continue to ask questions of their healthcare provider in order to understand what to expect from the trial (16).

The implications of improving patient involvement can be gauged from figures provided by the National Cancer Institute (NCI), showing that approximately 5% or 40,000 to 45,000 cancer patients are enrolled in clinical trials at any given time (16). The American Cancer Society (ACS) has highlighted the benefits of participation in clinical trials, citing that around 90% of children with cancer are participating in paediatric oncology clinical trials, compared to only about 3% of adult patients (17). This trend is believed to have played an important role in the medical advances in treating childhood cancers. The US Presidential Memorandum issued in 2000 was designed to extend to all types of clinical trials and also called for outreach programs, which would publicise trials to senior citizens (17). The Department of Health and Human Services also explored the possibility of establishing a national registry of Medicare-covered trials (17). The registry would describe types of trials in progress, participation rates and the procedure for patients to access the trials (17).

Many patient groups, particularly those in the USA, have become pioneers in educating the public with regard to clinical trials and it is in the interests of those developing new treatments to establish better links with them. On a long-term basis it is in everyone's interest to boost public confidence in participating in clinical trials through demonstrating the benefits.

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