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Thinking ahead for effective clinical trials

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As the complexity and expense of clinical development grows, there is considerable pressure on companies to maximize the potential of a clinical study.

A 2002 US pharmaceutical industry survey showed that, on average, clinical trials accounted for 40% of total R&D costs[1]. As the complexity of clinical trials and regulatory demands increase, the portion of R&D allocated to clinical trials will rise further. Yet with only 21.5% of drugs entering into phase 1 trials gaining market approval, the pressure on companies to improve success rates in clinical development is intense[2]. In this article, we will highlight some critical factors for the progress of clinical trials that should always be considered before proceeding. As clinical trials are run on a global basis, it would be impossible to cover every scenario in different countries. Nevertheless, as these factors are discussed, the examples provided illustrate the diversity of challenges that those embarking on clinical trials face.

No ideal solution

There is no 'one size fits all' formula for the correct strategy for clinical trials; each project has its own unique features that make comparisons with other trials difficult and potentially unreliable. The job of developing a realistic cost for the project, yet accounting for factors that can change it, can be daunting. The larger the project the more numerous potential problems can be.

With clinical trials, a number of factors come into play—everything from the nature of the compound, patient availability and recruitment, ethical considerations, study center and investigator suitability, geographical locations, local regulations, drug importation and labeling, market potential, and, of course, resources, timelines and costs. Those involved in planning and conducting clinical trials must balance all these factors and yet ensure that none of them act as a barrier to progress.

Although it is impossible to predict every factor that will affect the cost and conduct of a clinical trial, by thinking ahead, the major issues can be identified. Furthermore, any preconceptions can be challenged and alternative scenarios can be devised. It is essential that companies entering clinical development realize that the field is extremely competitive. Competing trials can cause many problems, particularly for patient recruitment, but by having a proactive approach, managers can devise contingency plans to deal with such situations.

Clear assumptions

Some clients new to clinical development will expect there to be an 'average price' for a clinical trial, but one does not exist and no one should ever rely on such a figure. A variety of factors can influence the costs of a trial; hence it is important that the company is clear about the assumptions it wishes to base the costs on and the services it is seeking. If the initial details supplied are vague, it will be difficult to supply reliable costs for a trial. The usefulness of a budget depends on the assumptions on which it is based.

If setting out initial assumptions is problematic, it is beneficial to ask those specializing in clinical trial development to set out the factors that they believe will be critical to the success of the project and how these will affect the costs. For example, if a trial is focused on a rare disease, patient enrollment will be difficult. A company would need to evaluate the cost implications of a lengthier time frame for patient recruitment. Similarly, if a clinical trial program covers a large geographical area, the number of monitoring visits needed would be an important part of the planning.

Sending monitors to distant locations can be expensive and these costs need to be carefully assessed beforehand.

Companies can outsource their clinical development work to contract research organizations (CROs) that specialize in clinical trials. As these organizations have experience running trials in different geographical locations, with differing drugs and therapeutic areas, they can offer objective advice on potential trials. It is advisable to gain the view of a number of CROs to determine who can provide the company with the best value.

A good way to prepare for clinical development is to carry out a feasibility study for the proposed trial in the global regions of interest. Various types of information can be sought, but typically the study might examine potential trial locations, investigator suitability and experience, and the frequency of patient referrals. This type of information can be obtained from investigators at study sites in the countries of interest. Some background information, such as epidemiology, can easily be assessed, by looking at the literature.

Striking a balance

Many costs are project-specific and so care should be taken in comparing them with costs for other types of trials. It is, unfortunately, all too easy to become obsessed with the cost of a clinical trial, only to find out that cutting costs reduces the overall quality of the project.

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Generally, companies will wish to market their products in the three main medical markets—the US, Europe and Japan—where clinical trials are run according to the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) standards. When extending their markets elsewhere, researchers should expect to run trials to a similarly high quality level. It is perfectly possible to do this, but companies must factor in how this will affect their future commercialization efforts. For example, India is becoming a popular location for clinical trials and data can be generated to the satisfaction of the US Food and Drug Administration and other regulatory authorities. The country can potentially offer advantages in terms of set-up costs and large patient populations.

However, if a company were to carry out its entire clinical development in India, based on cost, would it be able to convince US, European or Japanese doctors, when the product is eventually marketed, to use the product? Although the clinical data would be perfectly acceptable in a regulatory context, and the product recognized as safe and effective, doctors often feel more comfortable if some of the data had been generated locally. Medical practices vary from country to country and physicians will feel better able to relate to local trials of the product.

Furthermore, if a rival product has undergone trials in one of the major pharmaceutical regions (US, Europe or Japan), physicians may preferentially select it over the product tested only in India. Companies therefore tend to use a combination of major regions to allow doctors to become familiar with a product, and emerging regions to provide benefits in terms of cost and patient recruitment. However, some emerging locations, such as Mexico and China, have now become important pharmaceutical markets in their own right.

A company that relates the cost of its project to its eventual objectives is the most likely to succeed. For example, if a company wishes to run a trial in an emerging geographical location, such as Latin America or Asia, it will need to allocate greater costs for the travel involved in monitoring the trial, as the study centers may be far from the company location. However, if the region selected is beneficial in terms of fast patient recruitment, then this will reduce the impact of the extra traveling costs. Similarly, in Europe there has been publicity about the benefits of working in Central and Eastern Europe and frequently those unfamiliar with the region have assumed that it is 'cheap to work in.' However, this is not necessarily the case. It might be necessary to purchase specialized equipment for some Central and Eastern European centers, for example, and this cost needs to be planned for in advance. However, this should not discourage companies from conducting trials in these countries. With the right approach, Central and Eastern European countries can offer fast patient enrollment rates and offset the initial costs for specialized equipment.

Going global

Patient availability and recruitment is an issue that is high on the list of factors affecting a project's timelines. In some cases, because patient recruitment can be difficult, particularly in the face of competing trials, companies have extended the scope of their trials to include emerging pharmaceutical regions such as Asia, Latin America and Africa. Although clinical trials are now taking place in diverse regions across the world, companies face numerous new challenges when incorporating emerging regions into their clinical development plans. In North America, Europe and Japan, the regulatory, ethical and clinical research environments are fairly well defined. However, with emerging regions, these environments are less clear-cut and guidelines acceptable elsewhere may not necessarily apply.

Companies running clinical trials in emerging regions will need to carefully select the centers and investigators to ensure that ICH-GCP standards can be maintained. In addition, they will need to carry out thorough training

and monitoring to ensure that these standards are followed. Proactive management of sites is important to eliminate or minimize events that would have an effect on the smooth running of the study and cause delays or quality problems. Frequently these will be related to the inexperience of the investigators in participating in a large international study. Although such investigators are often enthusiastic, they may need adequate support and guidance to meet the necessary quality requirements for the study.

Central and Eastern European countries can be useful locations when conducting trials in specific therapeutic areas and many of the countries in this region are well respected for the high quality of their clinical data. Over the last decade, the number of multicenter clinical trials performed in Central and Eastern Europe has grown at an average annual rate of 30% (ref. 3). For example, Table 1 shows the number of trials performed by Western companies in the Ukraine between 1999 and 2002 (ref. 3).

Conditions may be present that are infrequent in more economically developed parts of the world. For example, there are populations in the north of Russia where types of liver enzyme deficiencies are more prevalent than in other areas of the world. In addition, because of the Chernobyl accident, certain types of cancer have appeared in the region in clusters, and chronic obstructive pulmonary disease is often present in mining areas because miners do not always have protective measures in place. Furthermore Central and Eastern Europe offers a highly specialized, centralized healthcare system that provides access to a large patient population that is concentrated in a limited number of centers.

Other emerging regions of the world, such as Latin America, Asia and Africa will provide similar advantages to certain projects. Referring to international databases containing health statistics, such as those from the World Health Organization or the United Nations, often reveals regions that have large patient populations with particular diseases.

Patient recruitment planning

Companies should always proactively identify sites that will be good at recruiting patients for clinical trials. Table 2 shows some issues that sponsors need to consider. Recruitment plans, which each center completes and signs, are particularly valuable. The recruitment plan states where the investigators will find patients for the proposed study and the timelines. Written recruitment plans make the site more accountable and encourage centers to consider their recruitment strategies early in the study.

As indicated previously, contingency planning can be beneficial. Centers should provide lists of patients eligible for the study and who have agreed to participate in principle, which should agree with the numbers in the recruitment plan. If the center provides this list before the trial is initiated, a trial commitment fee can be paid to recognize the investigator's time and commitment. Table 3 presents some examples of contingency plans to enhance patient recruitment.

Regulatory affairs

Companies must always carefully assess the regulatory implications of their clinical trials strategy. Not only can it have a major bearing on timelines for a project, but it can also affect the cost. Regulatory affairs is a complex and ever-changing field and so it is essential to gain insight from experts in this area to ensure that the correct approach is used for the countries of interest and for the product being developed. Companies accustomed to dealing with a particular regulatory agency can find that changing countries can dramatically alter the regulatory strategy and the time involved in gaining approval for their trial.

For example, although each state in the EU has its own variations in how clinical trials are run, the EU Clinical Trials Directive (2001/20/EC), which came into force on May 1, 2004, is fundamentally changing the manner in which clinical trials are carried out across the EU. The two main objectives of this directive are to provide a more harmonized structured EU regulatory framework and to ensure that the safety of clinical trial patients is specifically addressed in such legislation across the EU. Therefore, companies must have an understanding of the impact of the EU Clinical Trials Directive. Despite the widespread media coverage of its implementation, six months after the deadline some EU countries had not implemented (such as The Netherlands) or had only partially implemented (such as France) its provisions. Thus clients running clinical trials in Europe must factor in the additional expense of regulatory support for keeping up with changes. During the transition period for the EU Clinical Trials Directive, companies may believe that the processes are unclear, but as countries define their national legislation there will be advantages from the legislation in terms of standardized processes. Therefore it is essential for companies to keep up to date and relate changes to their project objectives.

Similarly the regulatory approach may vary for different types of drugs. For example, in the Netherlands, a biotech compound undergoes additional regulatory steps when compared to a standard pharmaceutical product. In other European countries, such as France, these additional steps are not a feature of the regulatory process. However, this does not mean that the Netherlands should not be used for clinical trials of biotech products, simply that the regulatory process must be approached in the right manner so as not to cause delays. The Netherlands is highly respected for clinical development and it may have benefits for the product in terms of patient availability and recruitment and investigators who are world renowned in their field.

Remaining objective

Although financial limitations must be placed upon a project, companies must focus on the 'cost-effectiveness' of a particular approach rather than cost alone. This is important when considering the future of the product being developed. If a company eventually wants to market a product in a major world market and hopes to convince regulators and medical experts of its usefulness, they will need to have excellent clinical data—and these are most likely to come from large-scale global trials.

A company that is clear in its objectives for its clinical trials and for the product being developed will be operating from a position of strength when it comes to the conduct of clinical trials. Allocation of resources, expense and time should all be geared to these objectives and flexibilities must be built into plans to circumvent the inevitable problems that will occur with a trial. No trial ever runs exactly according to plan, but with a proactive strategy, based on sound assumptions, a company will be able to achieve its objectives.

Table 1: Number of trials performed by Western companies in Ukraine

Year	Number of trials
1999	25
2000	41
2001	59
2002	100

Source: reference 3

Table 2: Outline of a recruitment plan

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

Table 3: Contingency planning

Select more sites (typically 20%) than required
Consider reserve countries
Set targets within recruitment phase
Assess inclusion and exclusion criteria
Learn from best practice at successful centers

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