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Investigator selection

Shirley Wildey

INTRODUCTION

The aim of this chapter is to introduce clinical research personnel to the importance of selecting the right investigator and team for a clinical trial in order that the trial is conducted within agreed timelines and to the highest standards. Time spent on obtaining meaningful feasibility information and giving due consideration to the site selection process will be rewarded when the study is recruited on time with few drop-outs.

IDENTIFICATION OF INVESTIGATORS

Traditional methods

The important consideration when selecting investigators is to identify and recruit those who are competent and motivated to conduct the trial according to the protocol, within the agreed timelines and in compliance with good clinical practice (GCP) guidelines. Tried and tested over many years, the *traditional sources* for identifying potential investigators include company databases, marketing colleagues, literature searches and personal recommendation.

Company databases

Many companies have developed their own databases listing investigators by geographical region, therapeutic interest, clinical trial experience, research facilities and contact details. For many companies, this has become a global database that provides an opportunity to select investigators for international studies from a single source. It is important to take account of local data protection laws when storing personal data electronically, but this issue can be resolved by obtaining the investigators' signed agreement to their data being stored for the use of the company and its affiliates only. In some cases,

these databases are linked to an investigator website, allowing investigators to enter data directly to the database and to accept responsibility for the update of that information.

Provided that the database is kept up to date, it can contain a wealth of information regarding the performance of the investigator in previous studies for the company. In some cases, the database can be linked to a clinical trial management package to provide important performance metrics. These may include an indication of number of data queries raised at the site, number of protocol violations, enrolment data, and start-up times, i.e. the amount of time from study initiation to first subject enrolled. The database will also alert clinical monitors if there are any ongoing studies at the site (for their own or other companies) that could cause conflict problems, both with regard to clinical trial populations and to prioritisation of workload.

Marketing colleagues

Marketing and sales colleagues will be able to provide lists of 'good prescribers' for a particular therapeutic area. These lists can be used to send a mailshot to doctors to sound out their interest in taking part in a clinical trial. Such doctors may not be experienced investigators but they may have an interest in the drug. It is useful to be able to train and nurture inexperienced but enthusiastic investigators because they often become the better trialists. Sales and marketing departments will always be able to recommend opinion leaders. For some drug development programmes, it is common to have external consultants and opinion leaders assigned to provide information and advice and to lend a prestigious name to subsequent publications. These experts may be able to suggest other possible investigators with a particular interest in a study or to provide a network of contacts to recommend new investigators.

Literature searches

Literature searches of published works in journals or on commercially available databases may locate key centres or doctors with relevant research interests and be an indicator of successful completion of previous clinical trials. The editorial board listed on the inside cover of a journal will indicate eminent experts in a given disease area. Medical directories in most countries list information on specialties, location and personnel involved in health services, with some details of individual interests. Previously archived studies may also reveal information about potential new investigators. Lists of attendees and speakers at conferences and congresses may prove helpful for mailings about the study to generate interest from doctors. Likewise, attendance by clinical research staff from the sponsor at such meetings is a productive way of making contacts with potential investigators.

Recommendations

Current investigators already selected for a study may provide a number of personal recommendations on others who may be interested in the study, and a network of contacts can be developed in this way. Some investigators may suggest colleagues within the same institution or other doctors with whom they have previously collaborated on other studies. Tracking the career of a junior doctor who has been a good co-investigator on a study may provide a first-rate principal investigator of the future.

With regard to investigators who have worked on previous company studies, it is helpful to discuss the overall performance of their sites with the monitors involved in those studies. A monitor's evaluation of an investigator's study conduct can be the most effective guide to identifying good investigators. There is no better way to identify potential investigators than personal recommendation.

Alternative strategies

As the health care industry has progressed over recent years to providing more information in the public domain, *alternative 'web-enabled' strategies* for identifying investigators have evolved in parallel with the more traditional approaches listed above.

Surfing the Net

In the USA it is common to advertise studies to physicians on the Internet and this practice is growing in Europe. A number of sites have been set up to target physicians and give lists of studies in which interested doctors can participate. This is an excellent method of attracting motivated investigators who have a population of patients not previously used in clinical trials, and it offers an option to move away from the professional trialist.

Data mining from commercial databases

A number of commercial databases are available that analyse prescription data collected across countries or regions. From prescription information, it is possible to drill down and identify investigators with a high volume of potential patients, enabling those to be targeted who have a high throughput of patients with the condition to be treated. Data mining may also provide an opening for contacting doctors who have the required patients but who have not yet had an opportunity to participate in clinical trials.

Using investigator networks

Instead of selecting individual investigators, a Site Management Organisation (SMO) or an investigator network may be used. These are commercial, profit-

making organisations that provide groups of investigators or sites, and offer a centralised site management function with a focus on quality and efficiency of trial conduct.

SITE MANAGEMENT ORGANISATIONS

This section will describe the different models of SMOs and similar clinical investigator networks, and will consider their benefits and their suitability for undertaking clinical studies.

The SMO market place in Europe is relatively new and is expanding rapidly, currently accounting for a market share of 5% in clinical trial Phases II to IV (Getz, 1999a). The market place is not clearly defined and offers a mixture of models and practices, e.g. owned-site, network and hybrid. The type of model describes how the SMO operates in terms of identification, screening and recruitment of potential subjects. There are two basic varieties:

- The *owned-site* or *research site* model has its own centres where subjects are seen for study visits. The investigators may be employees of the SMO or contractors and will be supported by research nurses and administrative staff. In this model, it is possible to exert good management control of SMO sites. Subjects are recruited using a variety of approaches, e.g. database searching of referring practices and direct patient advertising. This model is particularly suitable for chronic stable diseases, e.g. osteoporosis, migraine, and hypertension but less so for acute diseases.
- The *network* model uses community physicians or general practitioners (GPs) as investigators, but again usually with the strong support of research nurses. The study visits are conducted at the GP surgery, with subjects recruited largely from the GP practice. This type of SMO has a regional coordination structure, offers site training/support, and quality assurance (QA) systems are in place. Subjects are recruited through database searches and following direct consultations with their doctor. In general, direct patient advertising is less effective in this model. The network model is particularly suitable for acute diseases, e.g. infections, and paediatric studies.

Other *hybrid* organisations exist alongside these two broad SMO models (Getz, 1999b). They combine aspects of both and are set up according to country-specific health care systems, culture and politics.

Most SMOs work in primary care and operate within a single country in Europe but the trend is for them to become multinational. Increasingly, some SMOs have also established links with secondary care, either for subcontracted services or as an additional source of potential subjects. A small number of SMOs work exclusively in secondary care.

Many SMOs originally specialised in a single therapeutic area, e.g. women's health. Almost all have grown beyond their origins and are now multi-

specialty operations. Generally, it is essential to consider SMOs, whether they focus on primary or secondary care, as capable of running studies in most therapeutic areas. In other words, a primary care SMO has the potential to run clinical trials in any disease area where subjects are actively managed by their GP.

SMOs can provide rapid start-up of studies across a network of sites. The protocol approval process is expedited because SMOs have developed relationships with and understand the requirements of ethics committees. They offer a single point of reference for all regulatory documentation. Importantly, they produce good feasibility for subject recruitment and routinely use a variety of recruitment strategies.

SMOs are a 'one-stop shop', offering a simplified process for negotiating contracts and investigator budgets. Instead of several financial agreements with all sites, the sponsor has a single contract with the SMO, which negotiates separately with its group of investigators.

SMOs will have their own standard operating procedures (SOPs) to describe their working practices and they provide efficient study management, with a project manager as the main communication contact. Their advantage over individual investigator sites is that they can be judged more easily on performance and quality and should be able to provide historical evidence of performance from previous similar studies, e.g. regarding data query rates and enrolment targets.

SELECTION CRITERIA

Now that the methods of searching for potential investigators have been identified, the selection criteria for the study will need to be defined so that a profile of investigator and site requirements can be built up.

Study phase

The study phase will dictate if the clinical trial should be conducted in a specialised clinical pharmacology unit or would be more suited to general practice.

Geographical location

The scope of the study will define whether sites need to be found in a single country, across several European countries or globally. Influence may be brought to bear by the marketing department to place the study in those countries where there is a priority for the product's current or future sales. The incidence of the disease indication in a particular country needs to be considered, with special reference to the local strategy for treating patients

with that disease. For example, diabetic patients are well controlled in most countries in Western Europe due to the nature of the health care system there. This is different from the situation in Eastern European countries where the diabetic patient population is less well controlled. This influences site selection because potentially fewer sites could be required in Eastern than in Western Europe to achieve the same number of subjects.

Primary or secondary care

The patient management strategy within a country will determine whether the clinical trial population to be studied is found in primary care or in hospitals.

Patient population

The investigator should confirm that sufficient patients are to be found at the site for potential recruitment into the study. As a rule of thumb, because investigators are often over-optimistic about potential subjects and may be unaware of how they fit the eligibility criteria, recruitment numbers suggested by the investigators themselves should be halved. Realistic patient availability needs to be assessed by thorough feasibility checks at the site: historical recruitment should be reviewed and any factors that may influence patient suitability must be addressed.

Timelines

The timelines of the study can affect whether an investigator can reasonably take part and make an adequate contribution to the study. The starting date may fall at a time when the investigator is on holiday or away at a conference and no medical cover is available. There may be a conflict with another study starting at the site. All such factors need to be taken into account when selecting a site. Clear definition of the study timelines will enable the investigator to ensure that there are no conflicts in undertaking to participate in the study. If the recruitment period is to be shortened, the investigators need to understand the implications for their sites, themselves and their staffing levels.

Facilities and resources

Any specific type of equipment that will be needed at a site, e.g. specialised photographic equipment for an alopecia study, must be defined at the selection stage in order to check site suitability. If the equipment is to be provided to the site, there needs to be adequate space to store and use it.

Similarly, the investigator must have sufficient staffing levels to provide the clinical and administrative support required for the study to be conducted to

the stipulated timelines. Investigators frequently underestimate the amount of work generated by a clinical trial and consider that their regular support team can cope with yet another study. Resources at sites may be constrained for many reasons, including competing studies, restricted timelines, anticipated high recruitment, or a high screening rate from advertising for patients. Such issues need to be discussed in depth with the investigator, and contingency plans must be drawn up for providing additional resources to the site, where necessary.

Regulatory constraints

Strong regulatory constraints may affect the ability of some sites and some countries to carry out the study. The length of time required for regulatory and ethics committee approval, both regionally and nationally, must be taken into account prior to investigator selection. If a study is seasonal, e.g. in seasonal allergic rhinitis, the approval time for the study may prohibit the involvement of certain countries if the resultant start date does not coincide with the start of the disease 'season'.

Financial arrangements

Although there are more important selection criteria, financial remuneration will inevitably be a deciding factor for the investigator. It is important to identify and exclude those investigators who are only interested in their own financial gain and who will participate in a study but may not produce the quality of data required within the stipulated timelines. Equally, fees need to be set at a level sufficient to reward investigators for their expertise and therapeutic specialism, and to encourage them to take part.

FEASIBILITY

To achieve the specified numbers of evaluable subjects, the selection of sites is critical to the success of the study. A good feasibility survey must be undertaken at an early stage in the selection process to ensure that a study can be conducted in the country or at the site of choice. The survey will gather and analyse data on the availability of potential subjects fulfilling the inclusion and exclusion criteria, realistic recruitment rates within stated timelines, current and comparator treatments, competitor studies, and regulatory and ethical issues. The initial feasibility survey may also check investigators for proven experience in trials in a particular indication. The questions asked must provide sufficiently well-founded responses to permit a decision on which countries and sites are to be used.

Good feasibility will make an immeasurable difference to a study. The monitor will feel confident about the site's capabilities and there should be

fewer drop-outs and fewer site replacements due to poor or no recruitment. The feasibility survey should complete those parts of the selection process that can be performed by telephone, fax and e-mail prior to visiting the site for a site selection visit.

SITE SELECTION VISITS

Although some investigators may have been involved in the feasibility survey, not all investigators will have been approached about the study beforehand. Initial contact with these other investigators is usually by letter, outlining the rationale for the study, the type of product and its stage of development, a brief description of the study design, the type of study population and measurements involved, the approximate time schedule, other products to be used in the study, and any particular treatment to be used. Investigators need to be provided with sufficient information to decide whether they consider it worth proceeding to the site selection meeting.

It is essential to remember that collaboration on a clinical trial may last for several years and that establishing a good relationship with the investigator from the outset is of paramount importance to the success of the liaison. A telephone call to the site will confirm the correct form of address, not only with the investigator's correct title but including key qualifications.

Once an investigator has expressed interest, a confidentiality agreement, a summary protocol and other relevant information will be sent, and arrangements made for the site selection visit. Prior to the visit, a letter should be sent to the potential investigator, confirming the arrangements for the meeting, including an agenda for the discussion and indicating whether any other members of staff need to be present. It is also courteous to suggest the approximate duration of the visit to allow the investigator and site staff to book sufficient time in their diaries.

For optimum results, the meeting should be a two-way process in which the monitor needs to impart information to and obtain information from the investigator so that the latter's suitability can be assessed. Therefore, good verbal and non-verbal communication is vital to encourage the sharing of information rather than a one-sided presentation to the investigator.

Monitors must meticulously prepare for this first visit by familiarising themselves thoroughly with the preclinical and clinical development of the trial product and by re-reading the protocol to ensure that they feel confident about discussing it. It could be advantageous to provide a short summary of the investigator's brochure. The monitor should know the investigator's background and be *au fait* with the investigator's research interests, recent publications and any other facts that might lend a broader perspective by which to judge suitability. Such preparation will also help in developing a

professional relationship, as the investigator will feel flattered at the interest shown.

The monitor must be absolutely clear on any aspects of the study that are not open to negotiation and on any study features that must be complied with by the site. It is important that these non-negotiables are emphasised during the site selection visit and that the investigator clearly understands their importance. Frequently, there can be pressure to recruit investigators too quickly, with the result that they are accepted as participants despite reservations about their commitment to the study schedule, for example, or to the number of subjects required.

The agenda for the site selection visit should cover the following points:

- Introduction to the study drug, including pharmacology (animal and human), toxicology, clinical development and regulatory status. The 10-minute summary of the investigator's brochure is useful at this point.
- Protocol review, focusing on eligibility criteria, randomisation/treatment allocation, safety and efficacy, adverse event reporting, required equipment and procedures, enrolment periods, treatment periods and follow-up visits.
- Discussion of subject recruitment issues, including estimates of the number of potential subjects who would be eligible for the study based on retrospective data over a specified time period. The investigator should be able to provide documented evidence, e.g. a database listing or clinic lists, where possible. The timelines should be discussed in detail, as should the obligations of the investigator to recruit the required number of subjects within those timelines. The meeting should establish how subjects are to be identified for participation in the study, e.g. from advertising, referrals from colleagues, etc. Similarly, the recruitment strategy needs to be defined in terms of whether the site will recruit in cohorts of subjects or in a steady flow.
- Case record forms (CRFs) and their completion.
- The qualifications of the investigator and support staff should be reviewed, together with the investigator's experience with similar studies and other clinical trials, particularly to identify any areas of potential conflict. The amount of resource available at the site must also be confirmed in case contingencies need to be developed to provide extra resource in order to carry out the study at the site. The responsibilities of the ancillary staff, e.g. pharmacist or dietitian, will also be identified and agreed at the site selection visit.
- The facilities at the site must be assessed as to their suitability for the study. This assessment should check the availability of special equipment and procedures for calibration and inspection, according to the manufacturer's schedules. Central/local laboratory requirements must also be reviewed at this stage.

- GCP and regulatory issues must be covered, including the informed consent process, investigator responsibilities with regard to GCP, insurance and indemnification issues, and regulatory approval.
- The name and address of the central/regional independent ethics committee (IEC) must be identified, and details of the approval process, including submission dates, must be discussed. The impact of ethics committee approval on the start date of the study will be clearly emphasised.
- The monitoring process must be explained, including frequency of visits, site contacts, availability of space, and source data verification (SDV) procedures.
- Arrangements for the study drug must be checked, including storage, handling and accountability. These aspects may be discussed with the appropriate site personnel, e.g. the hospital pharmacist.
- In reviewing the financial aspects, it is important to be clear whether the payment is a flat fee per subject or if there is some flexibility to negotiate with individual sites.

It is unlikely that all issues will be resolved at this initial meeting and a note should be made of any points outstanding that need to be dealt with, either before or at the study initiation meeting (*see Chapter 12*).

Following the selection visit, the monitor needs to consider critically the information collected in order to assess the suitability of the site for the study. Other colleagues involved with the study may be consulted in this process before making the decision to proceed or to reject the site. Although it can be embarrassing, the rejection of a site is not usually a major problem provided that the study specifications have been carefully explained at the outset. If there are any doubts over the suitability of a site, a decision to reject may be more appropriate than to proceed with a site that is not fully committed to the study. The monitor should not be forced into a decision because of time pressures or having to select a certain number of sites, otherwise sites that are not completely suitable will be included simply to make up the numbers.

Once the decision to continue has been made, the monitor should write to the investigator, informing him/her of the decision, detailing any agreed actions, and outlining the important issues and (if appropriate) the date of the next meeting.

INVESTIGATOR MEETINGS

It has become accepted practice to bring all investigators and support staff together for a joint meeting prior to study initiation. These meetings are an opportunity to explain GCP, the practicalities of the investigators' responsibilities, procedures for serious adverse event (SAE) reporting, CRF correction and query resolution, SDV and auditing. Investigator meetings provide an ideal platform for training the investigator in specific study procedures (e.g.

completion of rating scales), or for demonstrating study-specific techniques or systems (e.g. electronic data capture). Discussions amongst the assembled group of investigators can often identify problems with the protocol or other issues that have previously gone unnoticed. The meetings should address practical issues within the study, reinforce timelines, and be a good team-building exercise. If they are well conducted and held in a good location with excellent social arrangements, such meetings can be a key motivator for the investigators and a valuable public relations opportunity for the sponsor.

RETROSPECTIVE REVIEW OF THE SITE

Once the study has been completed, it is useful to review how the site has performed. Performance metrics are informative and provide a good indicator for selection of the site for future studies. It is useful to consider the requirements of the study at the selection stage and then to compare them with what the site actually achieved during the study. Typical parameters for review would include subject recruitment numbers, timelines, number of data queries, number of drop-outs, quality of laboratory samples, and adequacy of staffing and facilities.

If the investigator met the timelines, if there were few drop-outs, and if a good rapport existed between the site staff and monitor(s), the site was well selected. If there were major problems in finding suitable subjects, despite reassurances to the contrary from the investigator, and if insufficient staff were available to conduct the study, the site was definitely not suitable and should be considered carefully before being selected again. In reality, most sites perform somewhere between these two extremes and sound judgement needs to be exercised to assess whether performance was sufficiently good for the site to be recommended for future studies.

CONCLUSION

The selection of successful investigators is a difficult and time-consuming task that requires sound judgement. However, it is a critical exercise affecting the entire clinical research project and should not be undertaken without adequate training and support. When careful consideration and time are invested in the process, it can be a major factor contributing to the successful outcome of the clinical trial.

REFERENCES

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