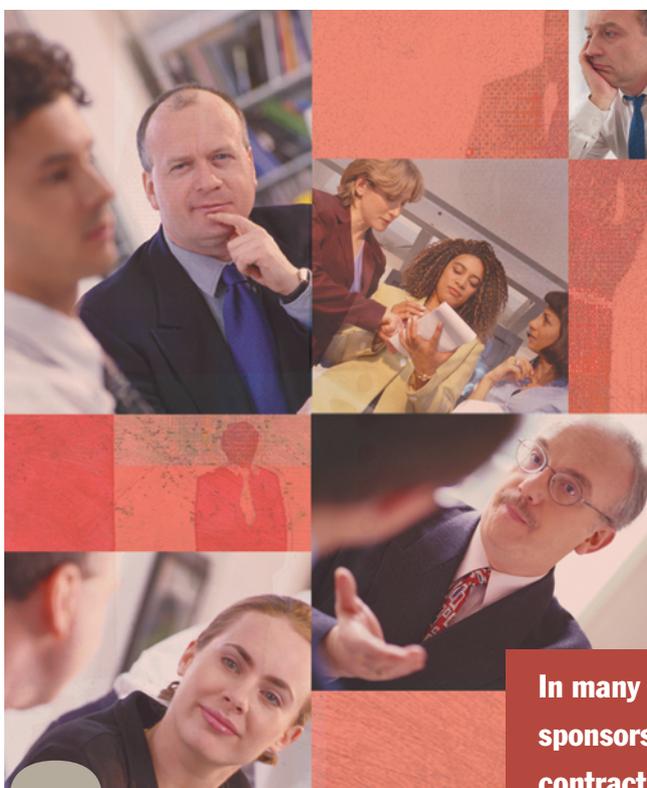


Selecting Sites and Investigators

An Approach for Central and Eastern Europe

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Poor selections can transform the life of a CRA into a nightmare.

When problems become serious, everybody involved usually tries to find out who is responsible for the unsatisfactory conduct of the study. Then they have to take corrective action, such as influence the investigator, recruit additional sites, close the problematic sites, and/or change the clinical research associate (CRA). Correcting errors once a study is running, however, can be far more difficult and expensive than preventing problems by rethinking the selection procedure, or even rebuilding it from scratch (see Rebuilding box). Involving local CROs or someone else with considerable local knowledge should be regarded as a necessary—if not always sufficient—step toward optimizing the selection procedure.

Our experience in managing clinical studies in Hungary and in the neighboring Central and Eastern European (CEE) countries has taught us the importance of capitalizing on “local knowledge.” We

have evaluated more than a thousand sites and conducted studies at several hundred. We believe that the qualitative and quantitative data we collected enables us to draw some general conclusions. Our perspective on the selection process is limited, however, to that of a CRO operating in the eastern part of Europe. Hence, we report here on problems with sites and investigators we find to be most frequent and typical in Hungary and some other CEE countries.

Our method is to first identify the dimensions that characterize the selection process, then to analyze our findings, and finally to seek the best practices to improve that process. The large variety of data we have collected aimed to evaluate site investigators, not to determine their relevance

In many CEE nations, sponsors must contract with institutions rather than investigators, which makes the system an important part of the selection equation.

Selecting investigators and sites is an important part of a clinical study. Both the quality of the medical data to be collected and the speed of its collection depend primarily on who collects it and the way they do it. Because sites and investigators are selected so early in the clinical development process, even the smallest mistakes can eventually become more important. Despite the importance of the selection process, many mistakes have been linked to it—mistakes that lead to a poor recruitment rate, lower quality data, and large numbers of queries.

to the selection process itself. One could argue, however, that the closer the rate of enrollment is to the predicted one, the better the investigator site. But I am cautious about drawing quantitative conclusions because of the complexity of factors that influence the rate of enrollment. To find a quantitative relationship between the rating of the center based on the selection process and predictability of enrollment, then we have to take into consideration the *ceteris paribus* clause. That is, all other factors being equal, what is the influence of site selection on subject enrollment?

One trivial example is an influenza study for which the precondition for starting the trial was the existence of a flu epidemic. But no such epidemic occurred in our country that year. Even if it had, the number of patients would have been determined primarily by the seriousness of the epidemic—which would have masked the predictive power of the selection process.

In other cases, studies were already running in a number of countries but the sponsors were dissatisfied with the speed of enrollment. In those cases, the goal was to enroll as many subjects as possible before the end of the enrollment period—regardless of how many centers had to be opened and the cost-effectiveness of that approach. In still other cases, a prolonged enrollment period made it difficult to define the denominator of

the enrollment rate (number of patients included over a certain time period). These examples prevent drawing quantitative conclusions based on the retrospective data.

Nevertheless, it is possible to draw qualitative conclusions based upon the key factors that link the selection process to the performance of the centers. We plan to design a questionnaire designed to reveal the way information collected during the selection process is correlated with the performance of the sites.

Problem areas

The problem areas that we found to influence the performance of sites investigators are goal setting, partner identification, and decision-making. All the pitfalls we encounter appear to be the consequence of errors in one of those areas.

Goal-setting. Goal setting involves the whole set of problems associated with one deceptively simple question: What does a good center or investigator look like? First, it is necessary to define *good*. We may all agree that a selection is successful if the site and the investigator selected do good work. There are, however, no good or bad sites per se. They can be assessed only together with the project's targets. So it is first necessary to determine what are—and what should be—the goals. Other questions one has to think about before beginning the selection process are: Who sets the goals? What are acceptable compromises? Surprisingly, one soon discovers that the answers are not at all obvious.

Partner identification. A clinical trial involves many stakeholders, including a sponsor, an investigator, often a CRO. Although the sponsor is a single legal entity, real-life sponsors are made up of different departments and individuals, including external specialists, safety committees, scientific boards, and other service providers. CROs act on behalf of sponsors, and often include departments similar to those of sponsor companies. Finally, equally important contributors to the big picture include the investigator and site staff, the hospital as a legal entity, the laboratory. During the selection process a CRA represents the sponsor (perhaps through a CRO) and interacts with an investigator. One might ask whether the CRA and investigator can represent the interests of all the stakeholders in a nondistorted way.

Decision making. Given the stakes for all involved, it seems obvious that it is important who is involved in the investigator site selection process and who takes the final decisions. Most problems arise from the fact that the “goal-setters,” the “executors,” and the “decision-makers” rarely try to reach consensus. Many times, the CRO doing a feasibility study doesn't know who the sponsor is. It is only when a selection is made that it has an opportunity to consult with the sponsor's representative. That is too late, and below I demonstrate what leads me to that conclusion.

Selection process

Goal-setting. As in the case of other basic notions in a clinical study, the fundamentals of the investigator site selection should be derived from the “constitution of clinical studies,” that is, the International Conference on Harmonisation Guideline for Good Clinical Practice.¹ The GCP guideline is very general on investigator selection: “The sponsor is responsible for selecting the

Rebuilding Checklist

With an understanding of the background presented in the article, you will be ready to rethink your selection procedure and, if necessary, rebuild it from scratch using this step-by-step checklist.

- Ask yourself about your long-term goals with the investigator site, and analyze whether your procedures fit the declared purposes. Avoid generic evaluation, because what is valid for one study and one situation might not fit another one.
- Identify as early as possible the person(s) who will take the final decision on the selection and discuss with the targets with that person.
- Add value to the feasibility phase or preselection process. Sponsors should pay for this and CROs should take it as seriously as the final site selection job. At least some of the potential sites should be visited and the potential investigators should be motivated to spend time and maximum attention on the study even at this stage.
- Using basic information about the study, design a study-specific questionnaire, weight and score the answers.
- Evaluate the investigator, evaluate the staff, evaluate the site, and evaluate the system as a whole.
- Design the right incentive system from the very beginning. Go even at the feasibility stage with estimated investigator fee data and try to figure out how this sum will be split between the institution, the investigator, and others. Reserve bonuses for high-speed, high-quality enrollment.
- At the end of the selection visits, don't be shy about suggesting sites different from those you suggested after a feasibility study or preselection activities.

TABLE 1 Analysis of Six Selection SOPs

Purpose	Selection Criteria	Counterpart Identification	Decision maker (based on)
1 Identifying potential Investigators Determining their suitability to conduct studies according to the ICH guideline	Initial interest, patient population, competing studies, staff, technical equipment, security and storage, working space for monitor	Investigator	Project Leader (personal visit)
2 Identifying potential investigators Ascertaining whether the investigator and center are suitable for the purpose of conducting the clinical trial	Qualifications, patient population, time, facilities, staff, interest	Investigator	Study project manager (PM) or experienced monitor. If no previous experience with the investigator, PM decides (by phone if previous experience within 12 months)
3 Identifying physicians who are interested in conducting clinical trials	Interest and abilities, experience, previous inspections, budget, anticipated workload, and conflicting studies	Investigator	PM or designee (not mentioned)
4 Selecting a center and sponsor	Qualifications and previous experience, population of potential subjects, time available for the study, well-qualified staff, interest, understands the importance of timelines; facilities and equipment, storage and security, working space for monitor	Investigator Trial Site	Monitor reports to PM, sponsor takes final decision (not mentioned)
5 Define the procedure for site visits To evaluate a site	Adequacy Patient population Storage/preparation facilities EC/IRB	None Describes the administration procedure of the visit (selection, monitoring, and close-out all together) itself.	Employee or designee (Not mentioned)
6 Selection of new investigators Establishing suitability of investigator and of site to conduct a clinical trial	Qualified by training and experience Potential to recruit Has time No potential conflict from other studies Facilities	Trial Site Investigators	Monitor (No visit if previous experience within the past 6 months New investigator: initial phone, then prestudy visit)

investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected” (5.6.1).

Section 4 of the guideline, under Investigator’s Qualifications and Agreements and Adequate Resources, we find somewhat more detailed descriptions:

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies). (4.1.1)

The guideline describes adequate resources in the same section: “The Investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period” (4.2.1). “The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period” (4.2.2). “The investigator should have available an adequate number of qualified staff and adequate facili-

ties for the foreseen duration of the trial to conduct the trial properly and safely” (4.2.3).

The ICH definitions give sponsors and CROs sufficient room to apply their subsets of criteria in the selection process. Their criteria are more or less projected in the standard operating procedures (SOPs) of the company that performs the investigator site selection. Table 1 presents examples of selection guidelines from six different SOP systems—each from a different manufacturer or CRO (including ours). It is intended to illustrate the dimensions of the selection process:

- The overall focus of the SOP and its declared purpose
- The selection criteria that the author of the SOP considered decisive for selecting a site or an investigator
- The basis for the selections of the decision makers.

A new approach

Careful reading of the goals reveals that most of the companies consider the selection process as being unidirectional (we→select→them). Contrary to this view, nowadays the burning question is “Who selects whom?” We read about² and observe more and more cases in which the investigator

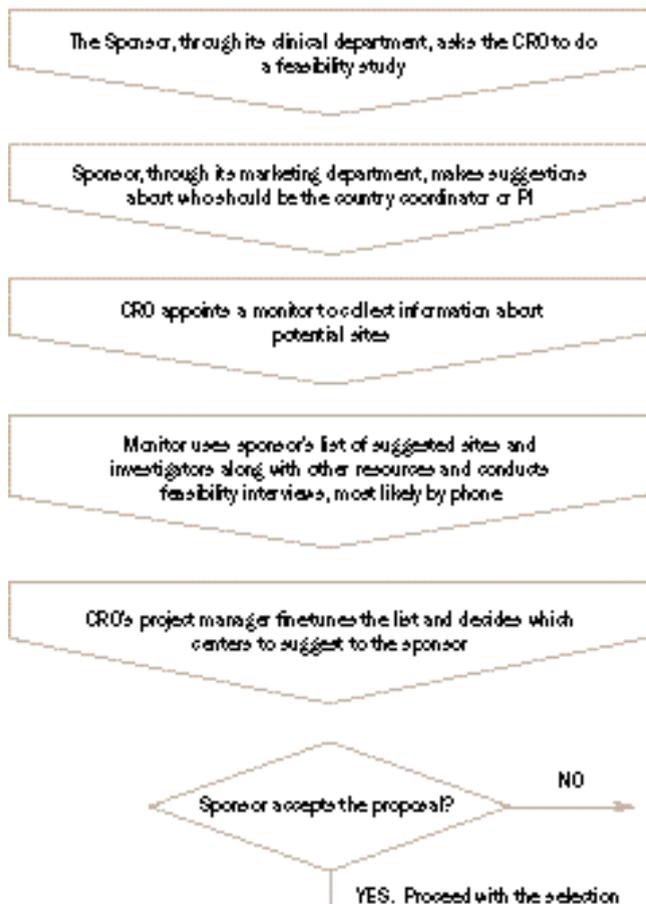


Figure 1. Events in a typical selection process.

reports having other proposals for competing studies and needing some time to decide which sponsor to select! Only the first and third SOPs appear to grasp that very important aspect, the commitment of the investigator. We should ask ourselves whether an otherwise perfect investigator really wants to work with us on a specific study. The time available for the study—pointed out as a selection criterion by almost everyone—is secondary to the commitment. If the investigator shows initial interest or if we can design an incentive that triggers interest, then an investigator will find time for the study, even at the expense of giving up something else (leisure, time with family, other research). We have time for what we want to have!

Looking at the goals also reveals that, although all of the SOPs describe basic “inclusion criteria” for investigators, none of them contain “exclusion criteria”—that is, factors that are the basis for deciding not to select a site. We suggest looking beyond the descriptions in the GCP guideline and the SOP for site selection. Instead, seek a real partnership with the investigator and the study team.

Inclusion/exclusion criteria. First, set clear inclusion/exclusion criteria describing what the ideal investigator should look like and the trade-offs you could live with. At the same time, be prepared to sell yourselves, to sell the sponsor, and to sell the study. Find out what expectations the investigator has, and decide whether it is possible to meet them.

Questionnaire. Next, design a questionnaire, fine-tune it on the basis of the discussion with the decision-maker of the sponsor

company, and, finally, assign possible scores and weights to the questions. Working space for the monitor may be important for example, but it is far less important than the experience of the investigator! A carefully worked-out scoring system permits you to deliver a final score for each site based on weighted scores for the individual criteria. Comprehensive questionnaires are widely used,³ yet few of them deliver a final quantitative measure of the suitability of the site. Questionnaires should be study-specific, otherwise it is not possible to evaluate what is perhaps the most important element—the initial interest of the investigator.

Partner identification. Table 1 shows that most companies—perhaps driven by what is described in the ICH guideline for GCP—focus on investigator selection. Few companies see selection as simply an administrative process. While the GCP guideline does, indeed, consider the selection process primarily an investigator selection process, it describes the suitability of a trial site only from the point of view of facilities, equipment, storage conditions, laboratory facilities, and the monitor’s workspace. The investigator’s knowledge and expertise is the factor of primary importance, followed closely by the quality of the site staff and its infrastructure. This concept comes from Western European countries, primarily from companies based in the United States. The contracts those companies propose are contracts between the sponsor company and an individual investigator. But such contracts don’t work in many CEE countries.

In many CEE countries, the institution or hospital is the legal entity with the exclusive right to sign contracts with sponsors. Investigators are simply employees of the institution. The institution assigns investigators to research activities in addition to their regular jobs and will award them some extra money for the extra work. Theoretically, the institution has the right to appoint the investigator, to withdraw that appointment, to appoint the study staff, and to decide on the way the investigator fee is split.

This status quo was inherited from the former social system of our countries, where the whole health care system—hospitals, outpatient facilities, and GP practices—was state-owned. Even today, when privatization in these countries is almost complete, most of the health care system remains state-owned. In a recent study, for example, less than 10% of the sites (cardiology outpatient facilities) were privately owned by the investigator.

CEE site selection

Because of the health care system, in CEE countries we select trial sites rather than investigators. Obviously, we select those that employ the investigators with whom we would like to work. While admitting that the key player in a study is the investigator—because the investigator’s knowledge and experience are of paramount importance in the treatment of the subjects—a process that considers only investigator selection is too individualistic an approach. This is true regardless of the ownership of the facilities.

The hospitals are not simply backgrounds—at least, they should not be—they represent a whole system. The quality of the pharmacy, the laboratory, the radiology department, and the ICU is important. Just as important, however, is the way they are functioning as a whole. Administrative, hierarchical, and personal relations among the functional units are very important. For example, we once lost a center where the investigator, the

TABLE 2 Short-term and long-term interests of parties involved in the selection process

	Short-term interests	Long-term interests	Comments
Sponsor Marketing Department	To have the clinical trials performed as quickly as possible (time to market!). The medication will be introduced /prescribed via the opinion leaders, so they should be involved in the study.	To have a high-quality product on the market with unique features that allows the sponsor to correctly position it vs. the competitors.	At the end of the day, they want to have turnover when the trial and the drug registration process is over. They are not interested in evaluating the foreseeable performance of the site/ investigator in the study.
Sponsor Clinical Department	To set a budget that would be approved and to remain within it. At this stage they would not like to spend money on a CRO's fight for the project. They would rather let the CROs compete for the project.	To have high-quality centers with high-quality personnel who deliver high-quality data. They would like to remain within the inclusion period and to have the fewest possible queries. For this they need speedy enrollment.	Investigator selection and CRO selection take place at the same time. They often ask more CROs to perform feasibility studies of the same protocol. They usually rely on the local expertise of the CROs; later, if the site selection report fits the feasibility results, they are happy because they have selected the right CRO (a CRO who delivers a consistent proposal about the sites and investigators is a good one, isn't it?) and they don't have to modify the budget because of a change in the number and location of sites.
CRO	CROs wish to use the least possible time and effort for the feasibility study, which typically is unpaid. They avoid travel and personal visits, and generally prefer simple phone/fax interviews. The more optimistic the feasibility report they deliver, the more likely that they will get the job.	Long-term goals are almost identical to those of the sponsor's clinical department. They prefer, when possible, that the sites suggested at the feasibility phase be those proposed for selection.	In most cases, at least during the bid period, they do feasibility studies at no cost. The more active a CRO, the more feasibility studies it does. Because sponsors typically pay nothing (or only a token sum) and there is no assurance that the CRO will get the job, CROs try to minimize the effort spent on feasibilities.
Investigators	During the feasibility phase they have no reason to refuse a study (unless it is professionally or ethically unacceptable). They don't want to spend (at no cost) too much time on the decision. Their best strategy is to appear enthusiastic and to give answers like "yes I can, yes I want to, yes, it's possible."	They want to deliver high-quality data because they want the sponsor to come back.	They are approached by many companies waving 2- to 5-page protocol synopses and asking them to tell something about their willingness to participate in the study.

hospital, and the pharmacy were all okay, but the investigator and the pharmacy were unwilling to cooperate, which jeopardized the study.

Legally, the sponsor must have a contract with the hospital. It is highly advisable to clarify with the investigator from the first moment who will sign the hospital contract, under which conditions, and what points the contract will cover—the language of the contract, the mode of payment, the governing law. The fee breakdown is another topic to discuss during the selection visit. The investigator is present in the hospital only for certain hours, but the subject might be continuously hospitalized. Physicians on duty, nurses not involved in the study, pharmacists dispensing concomitant medication might be also involved in the treatment of a subject. We learn of more and more cases where institutions allocate part of the income from a study to physicians who are not participating in the study, but for whom the study causes an extra burden.

In short, because of the site's importance, I recommend not only separate assessments of the investigator, the staff members, and the facilities, but also a sort of simplified system audit. It is worth knowing from the very beginning the level of cooper-

ation among the individuals and the units, how the site works as a whole. The sponsor's or CRO's counterpart is neither the investigator nor the site, but the system. A wonderful source of ideas on investigator and site selection, which should be incorporated into any SOP system, can be found in Spilker's classic *Guide to Clinical Trials*.⁴

Decision making. When a CRO (often several CRO subcontractors) is involved in a clinical trial, the events in the selection process typically flow as shown in Figure 1 (page 62).

Although I have not made a quantitative analysis, I have observed that—with a few exceptions—CROs come up with the same suggestions at the end of the site selection process as they did after their superficial phone interviews, perhaps by a relatively inexperienced monitor, and sometimes before the details of the study are known to the CRO. Sponsors, again with a few exceptions, approve the list. At first glance, this contradicts what all the SOPs suggest (Table 1): the necessity of a personal visit by an experienced monitor or project manager to make the right selection.

We could explain this process by the Retrospective Decision Model.⁵ In that model, decision makers attempt to rationalize

their choices on a retrospective basis. They identify favorites very early in the recruiting and choice process, but they continue to search for additional alternatives. Nevertheless, the implicit favorites are usually found superior to the alternatives because of perceptual distortion of information about the alternatives. The decision rule itself is being derived to favor the implicit favorite. Hence, although the decision makers are generally characterized as applying multidimensional decision rules, they often choose a favorite that is superior to an alternative candidate on only one or two dimensions. In the case of site selection, that means that once the CRO's project manager has delivered an initial proposal based on preliminary phone conversations, that during selection visits the PM will—usually involuntarily—observe only factors that reinforce the initial decision.

Some practical advice

Positive findings during the site visits will appear highly positive findings while negative findings will appear negligible. Later on, apparently minor problems that were already visible during the selection process, will cause most of the pitfalls during the study. The reason that many predictable problems remain hidden is that, in the short run, none of the actors wish to look for and find them. Short-term and long-term interests of the parties involved in the decision-making are shown in Table 2. Unfortunately, short-term interests often mask the long-term ones. Hence the outcome of the selection process depends on the long-term

vision (or myopia) of the decision makers.

Based on our experience in the CEE countries, we conclude that the most important factors influencing the selection process are goal-setting, partner identification, and decision-making. Considering the importance of the selection process, it pays to rethink that process and—if necessary—to rebuild it.

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