Site selection - identifying high performing clinical sites: An Insider's Insight

High functioning investigator sites are essential to the delivery of a successful clinical trial. But not all sites seem able to fulfil their study requirements. The critical question is how do you identify sites that are most likely to deliver your study on time, on budget and on specification?

Site selection, an often underrated and poorly understood discipline, has become a critical factor in the time taken and cost incurred in bringing new drugs to market. Since poor site selection can have an impact on study delivery (and possibly your short term career prospects) you want to be sure you make the right decisions. Whether you are a Sponsor or a contract research organisation (CRO), here we help you to focus on critical factors that will impact the success of your study.

Before you start

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Choices are often informed by data provided by CROs as part of a feasibility assessment conducted during the bidding process. However, there is a marked gap between the CRO's initial assessment of feasibility and knowing which sites will deliver your study to your expectations.

Preliminary site selection activities should begin once appropriate feasibility assessments have been performed.

One of the most important decisions the sponsor makes when embarking on a new clinical trial is the choice of the principal investigator (PI).

Prepare to succeed

Enrolling subjects is no simple matter. The inability of sites to live up to expectations is a growing source of frustration for all parties. Realistic enrolment projections are essential.

Once you have performed your feasibility exercises you will have a list of candidate sites. Collect all the information you need to decide which of the institutions to use in your study.

A short visit allows the Sponsor/CRO to confirm a site's capabilities and help secure consistent and high quality enrolment during the course of your study.

Some protocols can be complex in nature and although your investigators may demonstrate a good understanding of what is required, their operations teams may be less clear.

Key insights

Estimates suggest that recruitment difficulties account for up to 45% of study delays [1]. More than 35% of the sites will fail to enrol the number of subjects they indicated when signing up to take part in a clinical study, according to the Tufts Center for the Study of Drug Development (CSDD) [2]. This escalates development costs as the industry often responds to these challenges by engaging more sites than should be necessary. By anticipating that sites will underperform, study managers hope to minimise any delay resulting from having to identify and open new sites later in the study.

Making good choices when it comes to site selection is the key to reigning in such budget overruns and delays. But how do you know which are the sites with the characteristics best suited to delivering your study? Sponsors and CROs frequently use paper-based or spreadsheet methods. Choices are often informed by data provided by CROs as part of a feasibility assessment conducted during the bidding process. However, there is a marked gap between the CRO's initial assessment of feasibility and knowing which sites will deliver your study to your expectations.

Preliminary site selection activities should begin once appropriate feasibility assessments have been performed. Final site selection should only be formalised once the protocol synopsis or design of the study is clear and the required number of sites determined. After that, you can modify the study plans but the principal point of the synopsis should have been explained clearly to candidate sites.

Principal Investigator

One of the most important decisions the sponsor makes when embarking on a new clinical trial is the choice of the principal or coordinating investigator (PI). It goes without saying that they should be experienced and qualified in the disease area, but also have knowledge of running, coordination and leading clinical studies.

The role is not an easy one, and requires the individual to be both tough on fellow investigators and sufficiently engaged to help all parties navigate the myriad challenges that can arise during a study. It is also customary for the principal investigator to 'lead-the-charge' in recruiting patients, analysing data, publishing the results and speaking at conferences. However, for various reasons they don't always have the 'best' site from an operations or recruitment numbers perspective. For example, the notoriety of the investigator or site may mean that they are committed to other studies that compete for resources.

Site feasibility

Several levels of feasibility are necessary before a study can start. Often one of the first steps in any feasibility assessment is to identify the best countries in which to conduct the study. This assessment is generally performed by a CRO when it is compiling its bid – a precursor step that can influence the decision of study placement with a CRO. The CRO will often base its preference on their operational strengths but will also consider internal and environmental capacity, alignment of the clinical trial to the sites in terms of study design, dose of investigational product and patient type [3]. A robust and objective feasibility assessment is generally accepted as the best way to identify the best countries. There are commercial databases that can provide data to rationalise country selection (e.g., IMS Health's StudyOptimizer and Pharma intelligence's SiteTrove and Trialtrove – see table below for summary of reported usage [4]). As well as providing information on patient population densities for key diseases some also provide more specific data such as past performance of key sites.

Once the CRO and/or countries have been selected it is generally followed by a more granular feasibility assessment – using lists of possible sites/investigators who are invited to provide information about their capabilities and capacity. The request often takes the form of questionnaires (8 – 10 pages) sent to sites to identify interest and collect relevant information including an estimate of the number of subjects they might expect to recruit.

International Conference on Harmonization Good Clinical Practice Guidelines state that sites should demonstrate systematically their ability to recruit the required number of subjects in the agreed recruitment period. However, most sites don't follow any objective assessment process such as a review of local patient databases or registries. Generally, they provide a rough number based on their current patient population and how many they think they will recruit. It is generally recognised that such feasibility assessments are futile [5]. Sponsors and CROs are known to routinely mark down site recruitment projections to allow for over-optimistic predictions – often by more than 75%. Anecdotal reports from sponsor companies fit with the data from the Tufts Center for the Study of Drug Development (CSDD), confirming that even these 'adjusted' site feasibility assessments are poor guides to performance [2]. Site selection visits of candidate sites provide an opportunity to verify or even see past the data provided (see Site Selection Visits).

Tool/Solution	# Companies using tool
Internal tools, metrics, questionnaires	10
Citeline and Trialtrove	9
Clinical Trial Management Systems	6
IMS StudyOptimizer and SiteOptimizer	5
Feasibility tools, Qualification checklists	4
Investigator databank	2
External partners	1
Specific contact forms completed for each site	1
Transcelerate's Shared Investigator Platform	1

Enrolment

Enrolling subjects is no simple matter. The inability of sites to live up to expectations is a growing source of frustration for all parties. Realistic enrolment projections are essential. The number of eligible patients —and their motivation and willingness to participate in a trial—affect the ease and speed with which subjects can be found and enrolled.

Factors influencing patient availability include:

- Patient population epidemiology
- Success of current existing therapies for the target disease
- Restrictive inclusion/exclusion criteria and local legislature
- The competitive landscape (other trials targeting these patients)
- Trial awareness*

*Consider how to best employ project referral networks and advertising in advance of the study. Discuss recruitment procedures and mechanisms you might use with the site to ensure their buy-in.

Site selection - what do I need to know?

Once you have performed all your feasibility exercises it is hoped you will have a list of candidate sites. Do you have all the information you need to decide which of the institutions to use in your study? Areas you should feel comfortable with are:

Site infrastructure: Can the study team perform all the procedures themselves? Does the site have the infrastructure to fulfil all the activities specified in the protocol? If not, what are the costs or logistics of providing that equipment etc? Ask yourself how much it will slow or complicate study initiation or conduct if it relies on other departments in the hospital (e.g., pharmacy, imaging etc.).

Principal Investigator's publishing record: Investigators actively involved in research in the proposed field are more likely to champion early study completion, and may be able to identify other great sites. Not all your PIs need to be champions but having two or three sites that have enthusiastic PIs (depending on the size of your study) is helpful. Check these PIs endorse your proposed study design during planning – reducing time-consuming discussions and amendments later on.

Experienced staffing: What staff are available at the site to monitor the trial and ensure protocol compliance. What is their level of experience both with the protocol-defined procedures and study conduct (e.g., maintaining investigator files, completing eCRFs etc.)? How involved will the principal investigator be – will they delegate responsibility to a sub-investigator/study nurse?

History of similar trials (size and complexity): A site's history should always be reviewed to ensure it has previously been involved successfully in a study like yours. Check that their estimate for recruitment is on a par with previous targets (that they have hit) – can they share previous enrolment data? You should question whether there have been any major changes at site (since the last study) that may affect the running of the proposed study (e.g., changes in key personnel).

Site target disease understanding: Sites that specialise in your target disease are less likely to experience difficulties recruiting patients or implementing the trial protocol.

Registered target patients: Does the site currently have patients for the disease target under investigation on their lists? If so, how many? And how many of them do they plan to enrol in your trial? Does the site have any competing trials? If so, when will the on-going study finish and will those patients be eligible for inclusion in your study? You need to decide whether the site's involvement in any on-going studies should exclude involvement in your study.

Local disease demography: Time, cost and inconvenience of subject travel will impact on site recruitment and retention. Finding sites close to your target population is important when estimating how quickly you will achieve enrolment targets. Although it is hard to be anything more than subjective it is generally viewed that the more visits a study has, the closer their target population should be to the site. The importance of travel burden on recruitment and retention increases the greater the impact a disease or condition has on the patient and or carer.

Local competition: Having three sites in one city will most likely see sites competing for the same patient population. However, this is not always the case. In some countries, several centres of excellence are located close together (possibly even in the same hospital) because they are the only centre in that country that treats the condition.

Start-up cycle times lower than industry benchmarks: What cycle times does the site measure? For example, site activated to enrolment cut-off (a measurement of time to full enrolment of subjects to which the site has committed), enrolment cut-off to last patient in (LPI) – a measurement of the trials completeness. Are their statistics on par or better than industry benchmarks? These statistics are freely available in some countries. Are there institutional review or complex contractual requirements and will these affect your time lines?

Site selection questionnaires

Site selection questionnaires look a lot like study feasibility questionnaires and provide information to help you evaluate sites [6]. As with the feasibility process you can inform the site about the study, determine the site's level of interest and obtain statements and commitments. The site questionnaire thus needs to be designed as part of a larger process. A properly designed questionnaire facilitates the site's decision process. If the site considers the commitment associated with the study and realises it is not a good fit, everyone saves time. Empowering the site during this process helps build the relationship and may also elicit more honest answers.

A well-designed questionnaire can give a subtle insight into a site's complex personality. The questionnaire should arrive at the site with a cover letter, study summary and a description of the selection process. Care should be taken in how data are collected. True/false, multiple-choice and numeric answers are easy to read and tabulate, but they do not reveal the site's thought processes. Most sites can figure out the right answer. Elicit comments and allow space to elaborate on an overly simplistic answer. Responding to questionnaires takes time and so you should be considerate of the commitment the site needs to make to complete it.

It is unrealistic to expect a site's answers to your questionnaire to cover all points for all questions. It may be worthwhile splitting the questionnaire into two parts and holding the second part for sites that pass the first screen. Sequential questionnaires can introduce delays, but a short primer is more likely to be returned quickly. Two-step questionnaires may help attract better sites, which can be choosey about the questionnaires they complete.

The questionnaire is just one step in a best-practice process. They are a first step, identifying those sites you should visit (see Site selection visits).

Wherever possible, when assessing the responses to your questionnaire, take a data-driven approach to weighing selection and performance variables to aid in the identification of sites and target populations ideally suited to your study.
Establish a list of non-negotiable items – primary criteria that the site must fulfil to qualify for inclusion. Follow this with a secondary list of 'nice-to-haves' that you can score and rank on priority.

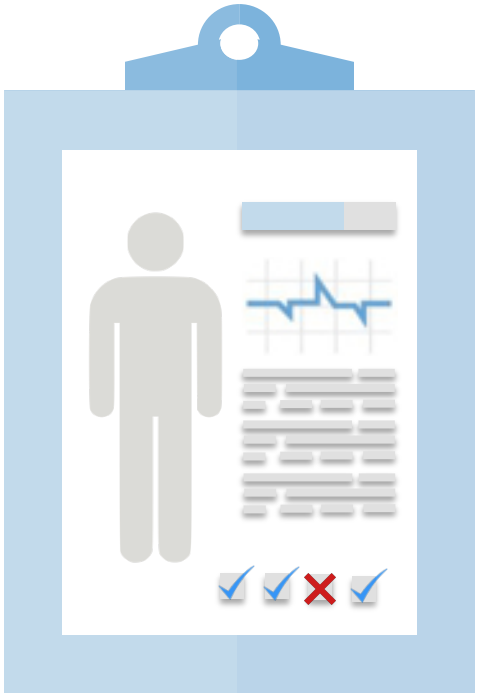
Primary criteria (must haves)
- Previous trial experience for PI
- High level of PI engagement
- Patient availability
- Previous history of achieving the required enrolment targets

Secondary criteria (ranked)
- History of similar trials
- Site infrastructure
- Start up time

Site selection visits

A short visit allows the Sponsor/CRO to confirm a site's capabilities and help secure consistent and high quality enrolment during the course of your study. These visits represent a critical event that sets the stage for an open, collaborative relationship to last throughout the study – imperative to the overall success of a study as many crucial tasks are accomplished during these visits. Where possible, take time to ensure that selected sites have the appropriate qualifications, staff motivation, patient population, infrastructure and support. Prepare yourself before the visit by asking for local knowledge of the site. Clinical research associates and/or monitors can provide essential insights such as the quality of data they provide.

An interview with our Head of Clinical Project Management

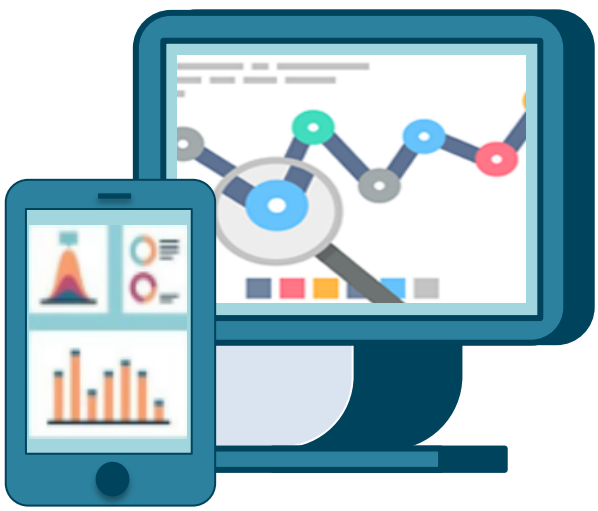


Q Why is site selection so complex?

A Site selection is both an art and science. The science comes from being able to accurately score sites on factors such as the expertise, capacity and capability. The art comes in being able to collate and weigh (from experience) the available information. The challenge for clinical researchers is to score these data objectively while placing an appropriate emphasis (weighting) on anecdotal (subjective) input and considerations of recruitment potential.

Q How can an experienced clinical project manager make a difference?

A Some protocols can be complex in nature and although your investigators may demonstrate a good understanding of what is required, their operations teams may be less clear. Dialogue with members of the team prior to any initiation meeting will give you a more realistic assessment of a site's ability to deliver. The secret is in asking the right questions of the right individuals at the right time. Often you get an instinctive feeling of whether or not the site is going to deliver during these discussions.



Q Shouldn't a feasibility assessment provide all the information I need to select my sites?

A One feasibility assessment alone will not provide you with all the information you need. There are various different types of feasibility that can be conducted and different measures to report [4, 7]. For example, if a feasibility assessment is conducted by a CRO when bidding for the study it is possible that its findings were matched to demonstrate a 'best fit' to the strengths of the CRO's infrastructure. It may mean asking investigators about their interest in the medical question being investigated, not just whether or not they have a -20 C freezer or how long their ethics committee review process takes.

Q How can I be sure that I am on the right track?

A There is a great deal of information available when considering sites and considerable advice on how to interpret it [3]. But there is no definitive solution – it is different every time for every study. You can always perform your own selection process using factors you feel are most important, construct a matrix, make your own notes and reach out for information from the sites themselves.

How are we doing?

The processes the industry is currently using to identify sites are clearly inadequate, since most sites underperform in terms of their contracted commitments, even after those commitments have been scaled back from estimates provided by the sites themselves [2, 8, 9].

Considerable resource is being committed to the process of selecting sites for our clinical studies. Research published in 2008 reported that site selection takes at least 3 months and can take as long as 6 months [3]. Factors impacting site selection timelines vary by therapeutic area, indication, geographic area, size, and phase of study. There simply may not be sufficient sites that meet all your required criteria. This is an increasing problem in many therapeutic areas, notably oncology. Companies conducting oncology trials typically report lengthy timelines as they rely on large academic sites to conduct their trials. These findings are comparable to those of earlier research examining first-patient in cycle time by type of site and by therapeutic area [4].

The type of site is also of particular importance, academic site selection typically takes longer than community-based sites. Academic sites have several layers of review, including institutional review boards or ethics committees and scientific review committees. Some larger academic sites in the US also have operational review committees, which can delay site activation and impact study start-up.

Study Rescue

Oftentimes clinical trials don't go to plan and sponsors start to believe that their study needs to be rescued.

Invariably the issues around why a sponsor would need a study to be rescued are focused on two critical site issues – poor recruitment or unsatisfactory data collection.

In practical terms rescue means that the original CRO is replaced with another. But, the CRO was not necessarily the reason for the failure. Most CROs claim to be experts in study rescue but will the new organisation be able to effect change in the sites?

> "Getting the site selection wrong will have a huge impact on the success of a trial. You will most probably not reach your goals and you will end up with delays and unplanned costs."

And finally....

There is no single 'best' site selection process. The method you eventually end up using will depend on the particular challenges you meet that will most likely be specific to particular features of the trial. There are some aspects that can always be improved, especially relating to the amount of data you collect – more data is always going to better inform your decisions (but only as long as you can find a way to process it).

Eventually you need to work directly with the people on sites and appreciate their challenges - there can be conflicts of interest between different parties such as the investigators, the clinical staff or the head of department. You can create some very scientific and technical tools to improve site selection but ultimately you need to deal with people.

One last point you may want to consider is embracing the concept of continual improvement. You could serve others once the study is complete by providing sites with a post-mortem of their performance by gauging areas for potential process improvements and providing insights on best practice. It may not help your company but it may help others down the line. If you are running a big study you could develop a regular newsletter to share information and drive improvement.

References

1. Lamberti, MJ, Mathias, A. Myles JE, Howe D, Getz K. Evaluating the impact of patient recruitment and retention practices. Drug Information Journal. 2012; 46(5): 573-580.
2. A Review of Patient Recruitment and Retention Practice Benchmarks Impact Report, Tufts Center for the Study of Drug Development, Vol. 15, No. 1, Tufts University, 2013.
3. Lamberti MJ, Chakravarthy R, Getz KA. Assessing practices and inefficiencies with site selection, study start-up, and site activation. Applied Clinical Trials, Aug 2016.
4. Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in Clinical Research, 2010; 1(3):106-109.
5. Getx K. Is Investigative Site Feasibility Feasible? Applied Clinical Trials; Jul 2008, Vol. 17 Issue 7, p36.
6. Goldfarb NM. Questions in Site Selection Questionnaires. J Clin Res Best Prac Vol. 5, No. 11, November 2009: https://firstclinical.com/journal/2009/0911_Site_Questionnaires.pdf [accessed 10 March 2017].
7. Insider's Insight into study feasibility testing, http://www.niche.org.uk/asset/insider-insight/feasibility.pdf 10 March 2017 [accessed 10 March 2017].
8. Reuter S and Esche G. How Effective are Site Questionnaires in Predicting Site Performance? J Clin Res Best Prac, April 2007, www.firstclinical.com/journal/2007/0704_Questionnaire.pdf [accessed 10 March 2017].
9. Goldfarb N. Reinventing the Site Questionnaire. J Clin Res Best Prac, May 2007, http://www.firstclinical.com/journal/2007/0705_Questionnaire.pdf [accessed 10 March 2017].

How can Niche help?

The Niche Clinical Project Management Team is experienced in translating feasibility data into successful operational networks through a balanced objective and subjective approach to site selection. I hope you found this Insider's Guide useful. We created it to share with you a few pointers and helpful key learnings that we have developed over our years of experience.

Please contact me at the email address below if you would like further help and advice on site selection for your upcoming study.

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