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# Critical Success Factors for Planning for Site Selection and Patient Recruitment Planning

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Effective site selection and patient recruitment practices present key opportunities for accelerating clinical trials. Proactive planning and a systematic approach can ensure a clinical trial's success. The critical success factors outlined in this article can help sponsors gain greater control over the factors most often cited for delaying clinical trials.[1] Important factors include efficient site selection, recruitment planning, and sophisticated protocol simulation techniques.

Successful subject recruitment is inextricably linked to a feasible protocol design and qualified, well-suited, well-managed investigative sites. External factors such as the regulatory climate and the competitive landscape affect study outcomes but may be harder to predict or control. Internal factors comprise both quantitative and qualitative aspects of study design: identifying, selecting, and managing sites as well as planning for subject recruitment and retention. "Factors That Influence Successful Study Outcomes" offers guidance for developing the protocol and planning site selection and subject recruitment sponsors should evaluate and consider all of those factors.

## Identifying and Selecting Sites

Successful site performance depends on many factors and is often equated with the ability to deliver qualified subjects and evaluable data within the agreed-on timeframe. Selecting the right sites will have a significant effect on your study outcomes.

Begin site selection by defining the qualifications necessary for a given trial. There is no such thing as an ideal site for all studies. Match the site characteristics to the specific needs of the study. Those will include qualifications and experience of the investigator and research staff, discussion of the technical expertise and facilities required for the study, access to the appropriate patient population, staff resource needs, and the ability to comply with all scientific, regulatory, and ethical site selection requirements. The Code of Federal Regulations and International Conference on Harmonization GCP Guidelines outline basic site selection criteria that must be fulfilled from a regulatory perspective. [5,6]

Once the ideal site characteristics are identified, prioritize them in terms of those aspects that are critical to study success versus those that are recommended but not imperative. A checklist that documents the criteria and importance level will help keep the information gathering and site selection discussions focused on the most important characteristics.

Once you have determined "what" constitutes your ideal site for the study, you need to determine "how many" sites to select, "where" they should be located geographically and "where" to find your potential investigators. Many factors such as disease prevalence rates, treatment practices, regulatory requirements and statistical considerations will influence the number and geographic distribution of sites.

Various resources exist to locate potential investigators, such as industry clinical trials listing and site selection directories, literature searches, faculty at teaching universities, directories of medical specialties, networking with sales/marketing/

**Factors That Influence Successful Study Outcomes**

| Protocol Design | Investigative Site Selection | Subject Recruitment |
|---|---|---|
| • Protocol consistency<br>• Study duration and visit schedules<br>• Nature, number, cost and complexity of study procedures<br>• Number, complexity and restrictiveness of eligibility criteria<br>• Ethical and regulatory considerations and approvals for all participating countries<br>• Sample size requirements<br>• Realistic enrollment goals and timelines<br>• Study value to sites and site execution difficulties<br>• Standard(s) of care and current therapeutic options<br>• Drug supply and availability<br>• Safety profile of compound<br>• Data collection requirements and procedures<br>• Investigator, study coordinator and subject feedback on study design to incorporate and balance scientific and practical aspects | • Sources of potential investigators<br>• Site interest, enthusiasm and buy-in to study design and rationale<br>• Site experience (clinical research and therapeutic area)<br>• Site staffing, resources, workload and time commitments<br>• Site personnel skills and abilities<br>• Staff turnover rates<br>• Functional responsibilities of site personnel<br>• Access to subject population with the required eligibility criteria<br>• Subject diversity requirements<br>• Technical facilities and equipment<br>• Computer savvy and accessibility<br>• Subject-friendly facilities and customer service approach of staff<br>• Reasonable and fair study budgets<br>• Ethical review committee policies and procedures<br>• Institutional legal procedures<br>• Site training and standard operating procedures<br>• GCP compliance and inspection (audit) history<br>• Past enrollment performance metrics<br>• Flexibility of clinic hours<br>• Role of key opinion leaders<br>• Country allocation requirements and procedures<br>• Site source document and data collection procedures<br>• Site security and storage facilities<br>• Site selection decision making process<br>• Role and accountability of CRA in managing site and subject enrollment | • Disease prevalence and incidence<br>• Real effect of eligibility criteria on subject availability<br>• Competing studies<br>• Subject motivations and barriers<br>• Sources of influence on study participation decision making<br>• Language and cultural issues<br>• Subject diversity requirements<br>• Healthcare system and referral / treatment approaches<br>• Subject and family / caregiver compliance<br>• Sources of potential subjects<br>• Recruitment, subject education and retention tactics and strategies<br>• Recruitment / retention budget<br>• Materials development and approval process and timeline<br>• Privacy regulations and protections<br>• Subject compensation |

***Table 1:*** [2, 3, 4]

contract research organizations (CRO), consultants and other colleagues, and so forth. "Select Sources to Identify Investigators" includes some examples.

Verifying site qualifications can be a timely, resource intensive, and intricate process. Sadly, it is a commonly accepted fact that only one-third of the sites selected will meet or exceed sponsor qualifications and that pretrial questionnaires may not be effective in terms of predicting site performance.[7] "How" you approach site selection will have a significant impact on the ultimate success of the study. A one-time feasibility survey is not sufficient in and of itself to thoroughly evaluate a site's qualifications. Short changing the process will guarantee poor results in the long run. Although all of the considerations outlined in "Factors That Influence Successful Study Outcomes" should be addressed in any site qualification assessment, it is especially important to gain an understanding of the research process and philosophy at the site. Questionnaires are ideal to capture objective data on the site's experience and past performance (For example, how many studies have you conducted? Have you ever been audited by the FDA? and so forth.) Attempt to validate the information provided in the questionnaire where possible. For example, if the site indicates that they have been audited by the FDA, request a copy of the audit report or, at a minimum, review the clinical investigator inspection list and classification (www.fda.gov/cber/compl/clininvlist.htm). Use open-ended and probing questions in discussions with the site. "Describe your informed consent process," "What concerns do you think your Institutional Review Board (IRB) will have with this study?", or "How will study responsibilities be delegated?" are examples of questions and statements that will allow you to ascertain the site's understanding of the clinical

trials process. Asking the same questions of the investigator and study coordinator independently can also provide valuable insight regarding the consistency of their responses.

Several individuals should be involved in various interactions with key site personnel over the course of several weeks. Information exchange may take place through telephone discussions, web and fax surveys, written questionnaires, and on-site visits. It may be important to stage the information gathering based on your prior knowledge and experience working with a site, whether this is a new therapeutic area or compound, and so forth. Initial site interest and experience queries may take place while the protocol is being developed. Schedule in-depth discussions after the investigator and staff have had the opportunity to review the draft protocol. Plan final verification during an on-site inspection of the research facilities. The information should be discussed in concert with a review of the Curriculum Vitaes of relevant research staff.

Gather information from investigators, site administrators/directors, clinical research coordinators, and other appropriate personnel including financial/legal, laboratory and pharmacy departments. Sponsor medical directors, project managers, clinical research associates (CRAs) and sales/marketing personnel will all have different insights to share about a site based on their interactions. Consider all perspectives and evaluate them in light of the prioritized list of site characteristics defined for the program. Don't underestimate the value of the qualitative as well as quantitative information gathered across and by the various sources involved in the information gathering.[8]

The process of site selection is both an art and a science. The better the quality of information gathered, the better the decision making. The more you can validate about the sites' access to the appropriate patient population, the higher the likelihood of enrollment success.[9,10] Effective site selection in combination with a robust recruitment and retention plan will have an even greater impact on study success.

**The Who, What, When, Where and How of Subject Recruitment and Retention Planning**

- **WHO**…is the target audience?
- **WHAT**…would motivate them to participate in this trial?
- **WHAT**…are the barriers to study participation and how will these be addressed:
  - — Protocol-related barriers
  - — Investigator (site)-related barriers
  - — Subject-related barriers
  - — Other barriers
- **WHAT**…is the competitive landscape? HOW…many competing trials are there that may impact enrollment?
- **WHAT**…are the regulatory and scientific issues that may impact perceptions about the product and ultimately influence a subject's willingness to participate in the study?
- **WHAT**…are the characteristics of an ideal site from a subject recruiting standpoint
- **HOW**… many subjects do I need and in WHAT timeframe?
- **WHERE**… will they come from?
- **WHO / WHAT**…is a potential source for study participants?
- **WHAT**…will be done to identify and attract subjects into the study?
- **HOW**…will the potential participants learn about the study opportunity?
- **WHAT**...tools and methods will be used:
  - — To raise awareness about the study?
  - — To enhance or supplement the informed consent process?
  - — To ease the burden of study participation (from the subject, family member, caregiver perspective)
  - — To ensure sites and subjects understand and comply with all the study procedures and drug dosing requirements?
- **WHAT**…approvals are needed for the strategies?
- **HOW**…long will it take for the materials to be developed, approved and produced?
- **WHEN**… will the strategies be implemented?
- **WHO**…will implement the plan? (WHAT…resources are needed to implement the plan)? WHEN...should you consider the services of a specialized patient recruitment and retention service provider (PRSP)?
- **WHAT**…will it cost?
- **WHAT**…questions will the subjects have and how best to respond to these questions?
- **WHO**…at the site is best equipped to address the subject concerns and
- **HOW**…should they be trained in subject communication skills?

## Recruitment and Retention

A patient recruitment and retention plan comprises all of the elements necessary for ensuring predictable patient participation in a clinical trial. The subject recruitment and retention plan has several goals. To ensure predictable participation in a clinical trial, sponsors need to:

- determine the most cost-effective and ethically appropriate way to build study awareness;
- implement effective patient identification and screening procedures to ensure that only those most qualified, interested potential participants are evaluated;
- facilitate informed study participation decision-making;
- employ appropriate processes and strategies to minimize dropouts without, in any way, coercing a patient to stay in the study;
- optimize the number of evaluable patients from which to generate the data necessary for a successful Biologic License Application (BLA).

| Select Sources to Identify Investigators | |
|---|---|
| Clinical Trials.gov | www.clinicaltrials.gov |
| Canada Trials: Clinical Research Center Profiles and Clinical Trial Listings | http://www.canadatrials.com/ |
| CenterWatch Investigative Site Identification Services | http://www.centerwatch.com/professional/site_info.html |
| Research Investigator's Source, Inc. | http://www.clinicalinvestigators.com/sponsors.html |
| Clinical Research Investigator DirectoryTM | http://www.criregistry.com/index.html |
| Clinical Trial Network | http://www.clinicaltrialnetwork.com/sponsors.php |
| Acurian | http://www.acurian.com/sponsor/siteRecruitment.jsp |

Each study has its own unique complexities and challenges. The more those can be identified up front, the easier it is to put in place programs and initiatives to mitigate those challenges. A recruitment and retention plan encompasses much more than tactics and strategies.

To start developing a plan, first thoroughly dissect the protocol. Determine which aspects of the study design contribute to challenges in identifying, educating, or retaining subjects.

It is also helpful to assess the competitive landscape. Determine how many competing trials are ongoing. Two helpful resources are the internet postings at www.clinicaltrials.gov and www.centerwatch.com. Those websites do not provide an exhaustive list of all possible trials, but they can give you a sense of similar studies that may be competing for the same population you wish to recruit.

Certain regulatory issues can have an impact on the public's perceptions of a clinical trial. Think about any similar drugs or biologics that were recently approved or withdrawn from the market. Consider new safety issues that have been identified for the class of medication you are planning to study. Explore those and other issues to gain important insights about the willingness of potential participants to take part in a given clinical trial.

Once you understand the potential barriers, challenges, competitive landscape, and regulatory environment, think about the target population. What are their needs?

To start developing a plan, first thoroughly dissect the protocol. Determine which aspects of the study design contribute to challenges in identifying, educating, or retaining subjects.

Who is a source of influence for subject study participation? What are their motivations to participate? Harris Interactive is an industry organization that periodically conducts public perception surveys about clinical trials opportunities and participation. The results of such surveys provide a general summary of why patients may or may not participate in clinical trials.[11] What are the unique considerations for your study?

It is also important at this stage to really define your target audience for the recruitment/retention plan. Although the study subject may be a child, the recruitment and education campaign need to target the parent. Or, for an Alzheimer's study, it may be important to target caregivers and ensure their participation, buy-in and involvement in the study. As you develop your recruitment and retention plan, you should also consider any special initiatives you will undertake to ensure diversity of the subject population.

The protocol will determine how many patients are needed. Generally that is described in terms of overall study goals for both randomized and evaluable patients. Depending on the phase of the study and prior experience you may have some preliminary assumptions about anticipated screen-fail ratios (for example, how many patients will need to be screened to enroll one patient). Additionally, you may have some expectations about number of drop-outs. According to industry statistics, a 25 percent drop-out rate is usual.[12] Your protocol will likely designate the expected number of patients required from each site to assure appropriate geographic representation of patients. Next, you must realistically ascertain how many patients each site can hope to enroll. Harper describes a framework and methodology to help sponsors and sites systematically determine the enrollment potential of a given site, and other vendors (such as Medstat; see www.medstat.com/1pharma/ctr.asp) use more sophisticated epidemiology, disease prevalence mapping, and prescription databases to further validate the enrollment predictions.[13]

Ascertain the percentage of patients that will come from within the study site's own practice versus external sources and what external sources will be used. Understanding how patients navigate through the healthcare system will be critical to understanding where to focus study awareness efforts. That will then lead to developing the specific study awareness tactics and strategies.

Clearly there are many channels for patients and families to learn about the study opportunity. There are many individuals within the site or healthcare system who may need to know about the study opportunity. Some studies should focus on awareness building in the public-at-large whereas other studies (such as in-patient studies) should focus on awareness within the site. Some studies will require a combination approach. Subjects who learn about the study opportunity through broad public awareness programs must, at some point, navigate the healthcare system. As those subjects encounter a healthcare provider or other source, a decision will be made as to whether to discuss the study opportunity with the patient or proceed with the standard of care. Clearly if the source isn't knowledgeable, the patient will never be aware about the opportunity to participate, or may be discouraged

## Selected Recruitment Sources and Strategies from "A to Z"

**A**
- "Ask me about research" buttons and badges
- Advertisements (all types of media)
- Advocacy groups
- Airport advertisements
- Allied Health Professionals
- Ambulatory care centers
- Awareness programs, to inform the public of alternatives for treatment

**B**
- Brand-name for clinical trial, to create recognition and association to the trial
- Brochures
- Bus advertisements
- Blimp ads
- Broadcast on local TV public affairs shows
- Billboards
- Bulletin boards

**C**
- Call centers, to support media campaigns
- Canvass college campuses;
- Chamber of commerce
- Chart reviews
- Church organizations
- Coffee shops
- Community centers
- Concert venues

**D**
- Database searches
- Dear subject and dear doctor referral letter templates
- Dinners for area physicians
- Direct mail
- Durable medical equipment (DME) stores

**E**
- Educational Materials, for both subjects and site personnel
- Educational seminars
- E-mail alerts and reminders
- Emergency Medical Personnel
- Emergency rooms
- Employee health clinics
- Employer "Brown Bag" Lunches at area employers
- Endorsement by the local community
- Exam table paper with study advertisement
- Exhibits and booths at events and conferences

**F**
- Fax alerts and reminders
- Festivals
- Fitness facilities
- Flyers
- Free health clinics
- Free screenings

**G**
- Gay and lesbian organizations
- Give aways (pens, post-it notes) with study brand and call center/site #
- Google advertising
- Grand rounds presentations
- Grocery Stores
- Gyms

**H**
- Health fairs screenings, as a part of community outreach and education
- Home health services (bring research to the subjects!)
- Hospital Employee Paycheck Notices
- Hospital ICD-9 and CPT code searches
- Hospital lobbies and clinics

**I**
- Indian Health Service
- Internet listing, Clinicaltrials.gov., CenterWatch, etc.
- Interviews with health reporters

**J**
- Journals, scientific publications on results of earlier phase trials with the investigational drug

**K**
- Key opinion leaders, to give credibility to study
- Kiosks (hospitals, colleges, etc.)
- Kits with recruitment materials

**L**
- Laboratories
- Laminated pocket cards with inclusion/exclusion criteria and study flowchart
- Leaflets
- Letters to potential subjects to investigate interest in study participation
- Libraries

**M**
- Magazine ads
- Malls
- Marketing research, to identify regions with high incidence of disease and prescribing patterns
- Mass media campaigns
- Mass transit advertisements
- Massage therapy clinics
- Media spots
- Medical society mailings
- Men's health clinics
- Minority outreach programs
- Movie theater ads
- Multilingual materials and site personnel

**N**
- Newscast – study can be featured during the evening news' health segment.
- Newsletters, both investigator and subject on status of study
- Newspaper advertising
- Nursing homes

**O**
- Occupational Health Nurses
- Occupational Therapists
- On-line advertising
- Outreach programs, providing support for subjects with specific disease indications

**P**
- Pain management clinics
- Payment for subject inconvenience as a method of compensation
- Pediatricians offices
- Pharmacies
- Physical therapists
- Post cards
- Posters
- Presentations and education seminars
- Press Releases
- Primary care physician offices
- Public health centers
- Public Service Announcements
- Public transportation advertisements

**Q**
- Quick-reference criteria pocket cards, which list the inclusion and exclusion criteria of the study, can be made available to the investigator and/or study coordinator to identify potential candidates.

**R**
- Radio advertising
- Referring physicians and healthcare practitioners
- Religious organizations
- Respiratory Therapists
- Restaurants and placemats
- Restrooms

**S**
- Sandwich boards
- Scheduling flexibility
- School nurses
- Senior centers
- Service organizations (Rotary, Lion's Club, etc.)
- Shopping centers
- Social Workers
- Spas and salons
- Special interest groups
- Speech therapists
- Sporting events
- Staff educational seminars
- Student newspaper and radio advertisements
- Subway advertising
- Support groups

**T**
- Taxi advertisements (receipts, panel ads)
- Technicians (e.g., EEG, ECG)
- Telephone "on-hold" messages describing ongoing studies at research center
- Training advertising
- Transportation program, for study volunteers
- TV advertising

**U**
- Urgent care clinics
- Universities/University dorms
- Unlimited coffee, tea, and milk for subjects in waiting room.
- Update investigators on any exciting new data with regards to the compound being studied

**V**
- Vans for clinic/hospital/elderly transportation
- Vendor, specializing in subject recruitment practices
- Videos (educational)
- Visiting nurse services

**W**
- Walk in a fundraiser walk such as Memory walk for Alzheimer's or a Breast Cancer walk and wear tee-shirts advertising your research office
- Websites (study-specific) and web advertising
- Weekly pager notifications
- Welcome kits, for subjects in waiting rooms
- Women's health clinics
- Word of mouth

**X**
- Xerox faxed announcements to sites
- X-ray clinics

**Y**
- Yahoo advertising
- Yellow book ads
- YMCAs
- Youth organizations

**Z**
- Zip code checks for disease prevalence
- Zoo advertisement (buy ads on zoo materials: maps, tickets, etc.)

**Source: Consolidation of ideas generated from > 200 subject recruitment workshops developed and facilitated by Beth Harper.**

from participating if the source cannot answer some basic questions about the study.

Development of the specific recruitment and retention strategies is the next step in the planning process.

This portion of the plan should focus on how to:

- educate the various sources, potential participants and their families about the study opportunity;
- raise awareness about the study;
- enhance or supplement the informed consent process;
- ease the burden of study participation (from the patient, family member, caregiver perspective); and
- ensure sites and patients understand and comply with all the study procedures and drug dosing requirements.

## Recruitment Techniques

There are endless ways of building study awareness and recruiting patients into clinical trials (See "Selected Recruitment Sources and Strategies from A to Z"). Certain strategies will be more effective with certain populations. Understanding the needs and motivations of the audience will help you prioritize your efforts. As discussed, some of the strategies are aimed directly at the potential patient population whereas others are more indirect approaches aimed at healthcare practitioner awareness and education. As you consider approaches for your recruitment plan, consider the following:

- Where are patients with a given condition likely to seek treatment information?
- Who else besides the patient may be involved in the decision to participate in a clinical trial?
- Where are they likely to seek health care information?

At a minimum, the recruitment strategies must comply with all appropriate regulatory and ethical guidelines. The FDA Information Sheet Guidances provide an overview of the recommendations for appropriate recruitment of study subjects.[14] Although the guidelines specify advertising, the principles apply to what is appropriate content for any type of direct-to-patient awareness materials such as posters, flyers, websites, etc. Each institutional review board (IRB) or Ethics Committee (EC) will undoubtedly have specific requirements and you should consult them as well. Generally speaking, all awareness and educational materials that will be viewed directly by the patient population should be submitted to the IRB/EC for review and approval prior to implementation.

**Retention Techniques Matched to Potential Study Participation Barriers**

| Study Participation Barriers | Possible Solutions |
|---|---|
| **Logistical** | • Flexible/convenient appointment times<br>• See subject immediately on arrival<br>• Appoint reminder cards<br>• Appointment reminder e-mails<br>• Stipend for transportation/parking<br>• Assist with transportation coordination<br>• Provide daycare support for working subjects<br>• Home health visits |
| **Educational** | • Provide coordinator contact information/pager for 24 hour availability<br>• Subject newsletters – information about disease/study progress<br>• Provide summary of lab results to demonstrate progress<br>• Plan to use primary language of the target population<br>• Use of minority spokespersons or community leaders<br>• Employ research staff who speak the language of target population<br>• Stress the contribution he/she is making to medicine and research |
| **Emotional** | • Spend extra time with subject each visit<br>• Written or telephone contacts between visits<br>• Pre-paid calling cards<br>• Birthday/holiday cards<br>• Small gifts/recognition items<br>• Subjects appreciate practical items for everyday use in particular |
| **Physical** | • Ensure subject sees the physician at each visit<br>• Provide summaries of lab reports or other health status information<br>• Provide alternate treatments or medical management<br>• Provide additional information about the study drug and safety profile |
| **Influencers** | • Provide health status updates to primary care (or other) physician<br>• Have PI contact primary care physician<br>• Invite family/caregiver to appointments<br>• Have PI contact family member/caregiver<br>• Provide general information about clinical trials and benefits of participation |

## Retention Techniques

Different approaches for retention are required in different therapeutic areas because the issues change depending on the disease, age, gender, and possibly ethnicity of the subject. Similar to recruitment techniques, the strategies for ensuring patient retention and compliance are unlimited; one strategy or approach does not work for all situations. When developing your retention plan, address the potential causes of patient attrition (such as, barriers identified), tailor your strategies to the particular patient profile, and of course keep in mind appropriate regulatory, institutional and ethical guidelines.

Although not intended to be all-encompassing, "Retention Techniques Matched to Potential Study

Participation Barriers" lists some possible strategies for overcoming various barriers to study participation and ensuring patient compliance in the clinical trial.[15]

### Documenting and Implementing

The rest of your plan will emerge from here in terms of budgeting and "operationalizing" the tactics and strategies you have developed. What materials will be developed and by whom? What will it cost to develop and implement the various strategies? What institution, sponsor, or ethics approvals will be needed? How long is the development-approval-production cycle time? What resources (in terms of personnel) are needed to implement the plan and when will the plan be implemented? When (or if) should the services of a specialized patient recruitment service provider (PRSP) be considered?

It is essential to document the plan in writing. There is no specific formula for how this can and should be done. Some individuals use a combination approach including Word documents for plan summaries, Excel spreadsheets (for the budget), MS Project or other timelines for depicting the tasks and timelines involved, calendars to highlight key milestone dates. Alternatively, all of the information can be consolidated into a PowerPoint presentation/executive summary.

Once you have developed the plan, it should be considered a "roadmap" to success but inevitably modifications will be needed along the way. Fluidity and flexibility are key when it comes to the actual implementation of the plan. Continuously monitor the plan and evaluate which initiatives are working and make adjustments accordingly.

### Protocol Simulation

Companies often run into significant enrollment problems during the execution of their clinical trials. The reasons for the problems, however, can be elusive. Attempts to diagnose the problem by questioning investigators (for example, during enrollment surveys or enrollment "booster" visits) are usually unsuccessful. Project teams sometimes resort to crash advertising campaigns and wholesale relaxation of inclusion/exclusion (I/E) criteria. Some trials have even been discontinued and restarted it in a different country or with different investigators, possibly with no better results.

Properly diagnosing existing and potential enrollment problems allows your team to eliminate the root causes, eliminate or improve low-enrolling sites, and drastically increase study enrollment.

Existing approaches for analyzing enrollment feasibility have significant limitations.

- Standard enrollment databases can detect enrollment problems only when the eligibility criteria are easily quantifiable and closely match those in the database. The use of proxy criteria makes the databases somewhat more robust, but creates a significant risk of inaccuracy.
- Independent enrollment consultants can help to predict enrollment patterns and identify appropriate enrollment strategies (for example, media buys), but would be unlikely to spot problems in a specific study that has complex enrollment criteria.
- Investigator surveys or brief investigator interviews are subject to the optimistic bias of the investigator, and therefore produce inaccurate results.

> You may find it beneficial to simultaneously benchmark the protocol against other, similar protocols . . .

Several new and sophisticated tools can be used to overcome such problems and successfully diagnose enrollment problems and remove their causes.[16] Unlike less sophisticated patient recruitment efforts, the goal is not simply to increase enrollment, but rather to identify the root causes of enrollment and other protocol problems and eliminate them. To do that, your study teams should combine in-person interviewing of a small number of sites with an execution simulation that gets to the root cause of investigator problems with recruitment and retention.

- Develop a detailed understanding of the most likely causes of a protocol's current or potential enrollment problems by way of a set of highly structured, confidential interviews with investigators/study coordinators and comparisons of study parameters to industry norms.
- Convene a simulation panel to help ensure that those causes (and other potential problems) have been eliminated and will not result in enrollment problems.

A Bayesian Interviewing/Probability Encoding technique can effectively identify the root causes of potential enrollment problems and the characteristics of high- and low-enrolling sites. Bayesian Interviewing allows the study team to remove the optimistic bias of experts such as clinical trial investigators and study coordinators when estimating enrollment and get true insight into potential enrollment, screen failure, and drop-out rates and how to improve them. They also get detailed data that can help the team identify in advance whether a site is likely to be a high- or low-enroller. Typically, only 6-12 site interviews are required to establish:

- objective enrollment forecasts (minimum maximum and average per site);
- objective screen failure rates;
- objective drop-out rates;
- types of sites to avoid and types to seek out;
- detailed characteristics of high- and low-enrolling sites that can be used by the team to predict the enrollment success of a given site;
- protocol characteristics (e.g., eligibility criteria, procedures or visit schedules) that are leading to low enrollment;
- protocol modifications that will result in enrollment, screen failure, and dropout rate improvement
- operational strategies (for example, advertising approaches, site locations and dispersions and protocol launch

timing) that will increase enrollment.

You may find it beneficial to simultaneously benchmark the protocol against other, similar protocols that have been performed across the industry. Using protocol databases such as Fast Track's PICAS, a set of protocols with characteristics similar to the one you are developing can be selected for comparison. That allows your team to see whether its protocol contains eligibility criteria or procedures that are more numerous or complex than those found in comparable trials.

A Protocol Simulation panel including protocol team members, local investigators in target countries, study coordinators, enrollment specialists, central lab representatives, CRO experts and others can identify many serious executional flaws in your protocol that might otherwise go undetected. The simulation participants use the benchmarking data, enrollment estimates, screen failure projections, and failure causes from Bayesian Interviewing/Probability Encoding as the basis of their protocol analyses. During a highly choreographed, one-day workshop, the simulation panel focuses on investigator selection/initiation and patient enrollment with the goal of heading off potential enrollment problems and ameliorate problems in ongoing protocols.

## Aim for a Competitive Advantage

Site selection and patient recruitment are complex processes that warrant adequate lead time, planning, resources, and investment. Data management and monitoring activities are also crucial to study success but without research subjects, there is no data to be evaluated. From basic methods to sophisticated protocol simulation techniques, biopharmaceutical sponsors can gain a significant competitive advantage by improving the quality and predictability of their site selection and patient recruitment planning practices.

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