A Strategic Formula to Enhance Subject Enrollment and Retention

Subject enrollment remains one of the most challenging aspects of clinical trials. As investigative sites explore new options to enhance success, they may consider a more structured "mathematical" approach. With the help of a simple formula, sites can engage in a comprehensive exercise that incorporates all of the elements needed to develop a well-planned initiative aimed at improving recruitment and retention.

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This formula is designed to focus on the careful balancing act between a site's need to enroll subjects in a timely manner and subjects' needs for information and respectful management throughout the trial. The equation, shown below, contains seven elements and is rooted in clinical trial jargon. It seeks to enhance enrollment and retention outcomes by keeping an appropriate balance between the perceived positive and negative aspects of clinical trial participation (CTP).

$$CTP = \frac{AE + CRC}{PI}$$

That is, CTP is a function of:

$$\frac{(\textbf{A}\text{wareness and }\textbf{E}\text{ducation}) + (\textbf{C}\text{redibility, }\textbf{R}\text{elationship, and }\textbf{C}\text{ommunication})}{\textbf{P}\text{eril (Risk) and }\textbf{I}\text{nconvenience}}$$

The equation is a convenient tool for highlighting vital elements of enrollment success, such as the subject's awareness of the study opportunity, the extent to which the subject is well-educated about clinical trials and the specifics of a particular trial, the credibility of the site staff conducting the trial, and other factors. This article explores each aspect of the CTP formula from the site's perspective, although sponsors and contract research organizations (CROs) are encouraged to follow a similar process when planning recruitment and retention programs.

The discussion describes the role of each factor in achieving a balanced formula in which the numerator (positive elements) increases while the denominator (negative elements) decreases, leading to increased likelihood of subject participation in a trial. Achieving this balance is a function of addressing the unique challenges of each clinical trial. For example, in one study, creating awareness of a clinical trial through a sophisticated advertising campaign may be less important than providing transportation to and from the investigative site. In another, establishing good communication with subjects through frequent contact may offset the fact that the study has sev-

eral long study visits. Once the strategy is hammered out and the plan put in writing, it becomes a working document guiding recruitment and retention efforts throughout the clinical trial.

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Determine Enrollment Potential First

Bringing the CTP equation into balance starts with a careful assessment of the number of patients sites can realistically enroll. When investigative sites agree to participate in a clinical trial, they are committing to the sponsor or CRO to fulfill an agreed-upon enrollment target. In fact, according to Section 4.2.1 of the Good Clinical Practice Guidelines put forth by the International Conference on Harmonization, the investigator should be able to demonstrate an ability to recruit the required number of subjects in the agreed-upon recruitment period.[1] But so often, enrollment falters because the site does not reach potential subjects or they drop out of the process.

The leaky pipe metaphor has long been used to assess the quality of the potential subject pipeline.[2] Frequently, sites miss the opportunity for a careful evaluation of the number of subjects needed to enter a "recruitment funnel" to yield the required number of enrollees. Making this determination is a function of identifying subjects to fill the pipe and then figuring where and why they are most likely to leak out of the process. As shown in Figure 1, if five subjects are needed, the site may need to identify 136 potential subjects with a particular diagnosis because it has to explore the reasons for the loss of subjects through the pre-screening, consent, screening, and post-randomization stages of the trial.

The leaky pipe analysis enables sites to identify the gaps and opportunities to either "fill the funnel" or "manage the leaks" in the most cost-effective and ethical manner. In some instances, the site will determine that it does not have the potential to recruit subjects from its own pool of patients, and that the cost and effort involved in recruiting using external sources will be challenging without adequate support from the sponsor. At other times, sites may determine that a robust retention program will be necessary to minimize drop-out rates due to preventable reasons.

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Figure 1 Funnel Calculator

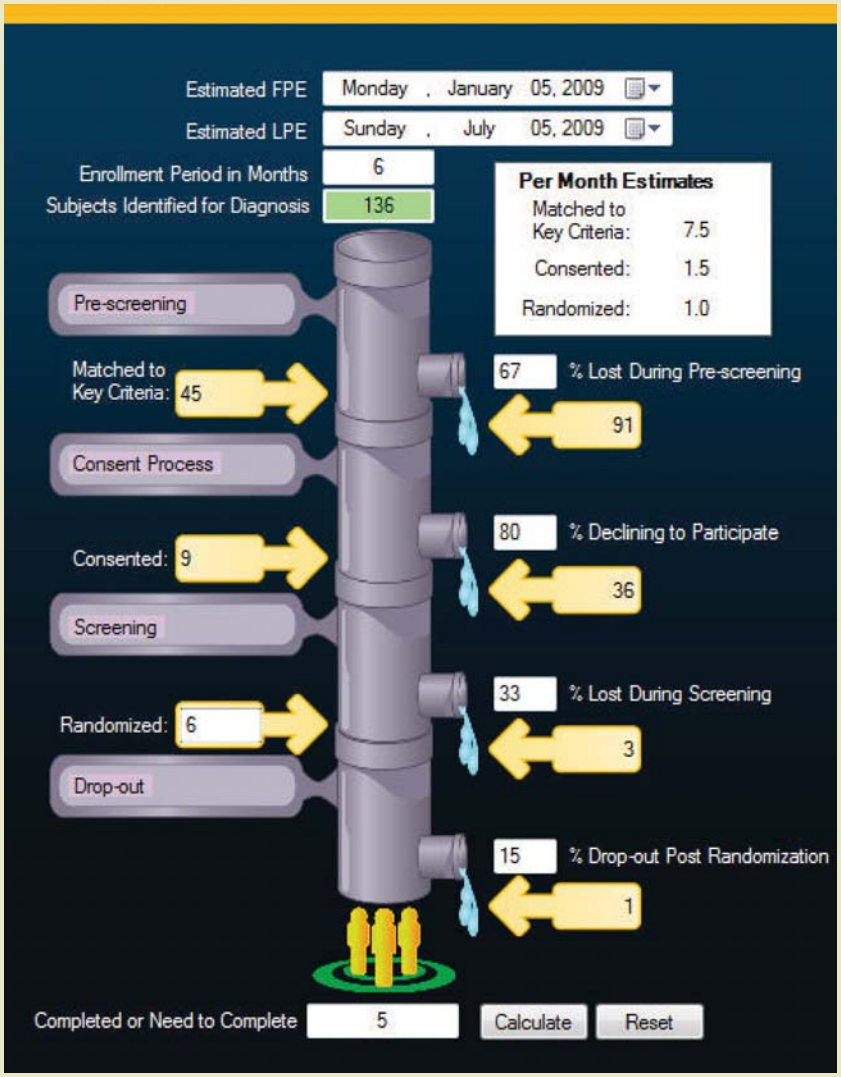

Photo courtesy of Synapse Analytics.

An honest discussion with the sponsor at this stage is critical to ensuring that expectations are clearly understood about the site's realistic enrollment potential and what recruitment and retention support services will be available. Sponsors prefer that sites respectfully decline the opportunity to participate in the trial if it is not feasible, rather than initiating, or worse, closing down a site that is overly optimistic in its enrollment projections.

Because this careful analysis is infrequently done, sites are sometimes unrealistic in assessing their ability to enroll, so sponsors may attempt to compensate by dividing the site's projected number in half or by a third. That effort does little, however, to clearly identify how many subjects a site can realistically enroll and retain. As a result, site performance still falls short, causing clinical trials to miss recruitment deadlines.[3]

Lack of awareness of clinical trials is a key reason why potential subjects do not participate.

If the analysis is performed, the sites can work toward bringing the CTP equation into balance by engaging in a recruitment and retention planning process that:

- Dissects the protocol;
- Creates a plan that addresses all of the common subject concerns;
- Documents the plan;
- Implements the plan; and
- Measures and evaluates the plan.

Awareness

Awareness, the first element of the CTP equation, may be defined as having the perception or knowledge of an event.[4] In a subject recruitment context, awareness suggests that subjects can be recruited for a clinical trial only if they have knowledge of it. Research indicates that lack of awareness of clinical trials is a key reason why potential subjects do not participate.[5] Changing this reality starts with the site sharing information about a study with the target audience—either directly or indirectly through the sponsor, CRO, or patient recruitment service provider—via various techniques that have been approved by ethics committees. This may include advertising, direct mail, distribution of posters and brochures in physicians' offices, and contact with national and local branches of patient organizations and associations.

Advertising theory suggests that a consumer must come in contact with a message three times before he or she will remember it.[6] If this theory holds true, in order for potential subjects to have a minimal level of awareness of a particular study, the site must bring it to the attention of the public at least three times.

Taking this notion one step further, different consumers are engaged by different types of messages through such diverse formats as print, television, radio, and Internet, so sites must decide the best vehicles for maximizing consumer awareness.[7] Applying these advertising principles to subject recruitment, it is possible to develop a new equation:

$$1 \times 3 \times 3 = 1$$

Keeping with the theme of marketing math, this equation translates into "One message presented three times in three different ways will be remembered only once." Consequently, there is a need for continual reinforcement of the marketing message, using different formats.

When using these principles to structure an awareness campaign, a whole host of questions must be answered to engage potential study volunteers, such as what is the target audience for the study, what is a potential source of subjects, and more (see Table 1). A discussion of awareness-building is not limited to these questions; rather they are meant to stimulate creative thinking.

"One message presented three times in three different ways will be remembered only once."

Often, awareness is equated with advertising. Although advertising is part of the outreach mix in numerous countries,[8] it should not take on heightened importance. Advertising that offers the right message in the right frequency and uses the right mix of media creates awareness, but it is only one of the seven elements in the CTP equation. If the other elements are not addressed or are "out of balance," advertising resources are wasted. For example, a well-thought-out awareness-building campaign will do little to secure enrollment if inadequate attention is paid to volunteers' concerns that the clinical study is too risky or too inconvenient.

Table 1 Questions Sites Should Ask During the Study Planning Process

- What is the target audience for the study?
- What is a potential source of subjects?
- What will be done to identify and attract subjects to the study?
- What are the most cost-effective ways to build and maintain awareness of the study?
- What methods/materials will be needed?
- What strategies and tactics will be used?
- What approvals are needed for the materials?
- Who will develop these and how much will it cost?
- When will they be developed?
- Who will implement the strategies and when?

Education

Educating potential subjects about clinical trials and engaging investigative sites to provide that education play a large role in enrollment success. Potential volunteers may become aware of studies through outreach efforts, but if they are not exactly sure what a clinical trial is or how one typically unfolds, they could be reluctant to participate. Subjects may have concerns about receiving placebo, or what their physicians think of the study.

To provide volunteers with adequate education, investigative sites need to ask such questions as who should be educated about the study, and what tools and materials are needed to supplement the informed consent document (Table 2). In addition, subjects should have access to resources that provide basic information about the disease or condition being studied, what they can expect during the first visit, and directions to the investigative site. Depending on the geographic location, materials might need to be in multiple languages. They may also need to be designed to accommodate visually impaired subjects.

Education about clinical trials should include a strong sense of cultural competency.

Educational materials should be subject-friendly and understandable in order to be of value to individuals of all levels of reading capability. Research suggests that the average American reads in the range of the fifth- to eighth-grade level,[9, 10] so educational literature should be evaluated for reading level using simple tools that are part of common word-processing programs.[11]

This approach can be applied to complex documents that the site needs to explain to potential volunteers, such as informed consent forms. A recent study indicates that informed consent documents are typically written at the college level and continue to expand in length.[12] To address this issue, the National Cancer Institute and many institutional review boards and ethics committees suggest that these documents should not exceed the level of eighth-grade (or international equivalent) difficulty.

In addition to improving readability of documents, education about clinical trials should include a strong sense of cultural competency. Simply presenting factual information to potential subjects about a clinical trial without the subtext of engaging them in a way that makes them comfortable does little to improve enrollment and retention. Policies implemented by the American Medical Association's Council on Ethical and Judicial Affairs stress the importance of understanding and appreciating cultural differences as related to delivering more effective healthcare.[13] Applying this notion to the clinical trial realm, it is essential for clinical trial professionals to be sensitive to how a subject's healthcare belief system influences compliance and satisfaction, two key elements that affect retention.

Table 2 Questions Sites Should Ask During the Planning Process

- Who needs to be educated about which aspects of the study (e.g., the subject, family member, parent, caregiver, treating physician)?
- What tools or materials are needed to supplement the informed consent document?
- What training is needed for site personnel? For subjects and families? For influencers?
- What are the most effective means of training these individuals?
- What questions will subjects have about the study?
- How well are site personnel positioned to respond to participant questions?

CRC: Credibility, Relationship, and Communication

Building awareness about a clinical trial and educating potential volunteers about the opportunity are only part of the enrollment equation. Just as critical is establishing credibility, building relationships with potential subjects, and mapping out a formal communication plan. The most well-thought-out awareness campaign and educational efforts cannot offset feelings of doubt by potential volunteers, or poor communication between subjects and the investigative site.

Establishing credibility starts by introducing the human element into the study. When a study volunteer walks into the investigative site, is there an air of professionalism? Are all staff members, including front-line personnel, aware of the study and do they know to whom to refer questions about the study? Have there been discussions about who at the site is best prepared to present the study and respond to questions from subjects and family?

These are questions that must be answered to set the tone for a positive clinical trial experience. Such questions also lay the foundation for building the kind of relationship that bonds subjects to the study and ultimately boosts retention. To start, all staff members need to be aware of studies at the site so anyone inquiring about them can feel confident that the study he or she is considering is important to the site. Nothing shakes confidence or destroys a subject's interest in a study faster than calling the site to ask about a particular study only to discover that the staff knows little about it.

A site also needs to be skilled in good customer service relations,[14] so that the staff knows how to make subjects feel valued and engaged. Always greeting them when they come for visits; providing parking vouchers; sending birthday cards; and calling, mailing, e-mailing, or text messaging volunteers to remind them

about upcoming visits are practices that create a sense of caring.

To improve customer relations, the site should establish standard operating procedures that foster consistency among the staff. This should include contact information for subjects' questions, a way for subjects to contact the site on a 24/7 basis, and a designated response time, such as not to exceed 24 hours.

Customer relations is largely a function of good communication, which is critical to interacting with study volunteers in the most effective way possible and is always focused on respect and cultural sensitivity. This entails hiring or providing access to multilingual staff, if necessary, and presenting materials in language that is understandable and translated as appropriate.

Peril (Risk) and Inconvenience

Two factors—peril and inconvenience—form the denominator of the CTP equation. The road to successful enrollment and retention is interrupted by barriers that, if not handled appropriately, can wreck the best recruitment efforts. Inconveniences such as no evening hours or inadequate parking facilities at the site are factors that can easily undermine the most well-thought-out recruitment campaigns designed to attract subjects in the first place.

To bring the equation into balance, it is critical to minimize those inconveniences and study-related perils if there is any reasonable expectation of the site enrolling in a timely fashion. Just as sponsors need to make studies subject-friendly by paying attention to the number and duration of visits and providing reimbursement for parking expenses, sites need to do their share by offering extended hours of operation and possibly providing round-trip transportation, meals, and activities for long study visits.

Managing risk requires several steps, starting with identifying the right person to present the risk/benefits ratio of the study. Just as important is having a qualified physician who is familiar with the protocol available on a 24/7 basis, as well as emergency contact information for the subject. In addition, the site should provide subjects with access to the most current study-related information in real-time through a website, e-mails, text messages, or phone calls.

Putting it All Together

The CTP equation is designed as a flexible formula that identifies the various aspects of successful subject enrollment and retention. Each element—awareness, education, credibility, relationship, communication, peril, and inconvenience—represents one-seventh of the formula, yet each may assume different degrees of importance from trial to trial and from country to country. One trial may require large amounts of education and relationship-building through the development of study-related materials and frequent communication, whereas another may need to minimize the inconvenience of multiple long site visits by offering lunch vouchers or child care.

To bring the equation into balance, it is helpful to map out a strategy for securing commitment to the study, identify the resources needed to support the plan, and determine roles and responsibilities for implementing the plan. Such activities need to be documented in writing in order to be appropriately managed. With this type of comprehensive approach during the planning process, sites have the potential to substantially improve their subject recruitment and retention practices and outcomes.

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