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Fixing the Protocol Feasibility Process

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When study sponsors assess the feasibility of a study, there are two parts to the exercise: (a) protocol-level feasibility (analysis of the study design) and (b) site-level feasibility, which is closely linked to the site selection process. Unfortunately, many feasibility assessments are not conducted in a thorough, consistent and systematic manner that accounts for real-world factors and supports process improvement from study to study.

This article will discuss:

- Common reasons feasibility assessments fail to result in predictable and timely study performance
- Differences between protocol- and site-level feasibility
- Recommendations for "fixing" the feasibility assessment process at both the sponsor and site

According to the Tufts Center for the Study of Drug Development, protocol complexity, site work burden, and the number of eligibility criteria have increased dramatically (Figure 1).[1] These increases require corresponding improvements in the feasibility assessment process because (a) protocols that are more difficult are also less feasible, (b) feasibility assessments themselves have become more difficult and uncertain, and (c) more complex protocols are inherently more expensive and time-consuming, so the stakes have increased.[2]

Figure 1. Growing Protocol Complexity[1]

	2000-2003	2004-2007	Percentage Increase
Unique procedures per protocol (median)	20.5	28.2	38%
Total procedures per protocol (median)	105.9	158.1	49%
Investigative site work burden (median units)	28.9	44.6	54%
Eligibility criteria (median)	31	49	58%

The Current State of Feasibility Assessment

Traditionally, protocol feasibility assessment has largely meant asking key opinion leaders and scientific advisory boards about the medical feasibility and scientific soundness of the protocol. Sponsors obtain little or no input from the investigators and study coordinators who will eventually conduct the study (or from potential study subjects). Instead, their views are collected, after a fashion, during the site selection process (and even later, at investigator meetings). It is asking a lot to expect sites to submit a questionnaire that demonstrates their ability to conduct a study and simultaneously gives thoughtful and honest feedback on the feasibility of the protocol. As a result, site selection processes usually fail at both objectives.

How can sponsors and sites make more informed decisions about the likelihood of successful study implementation? Protocol-level feasibility assessment should focus on the "red flag" issues that will most significantly determine success of the study, e.g., conflicts with standard of care, appeal to potential study subjects, and other practical aspects of study conduct. Site-level feasibility assessments should focus on whether the protocol is a good fit for a particular investigative site to conduct. For a given site, there must be investigator interest, an accessible patient population, suitable capabilities, and available resources when the study is to be conducted.

Figure 2 demonstrates the ineffectiveness of the current feasibility assessment and site selection processes, in terms of selecting sites that can predictably meet the enrollment goals. The Tufts report cited previously further reveals that the average study experiences two to three amendments. Nearly half of amendments occur before first subject/first dose in a study. Forty percent of amendments are completely unavoidable, but more than 33% are "somewhat" or "completely" avoidable (in other words, could have been anticipated and avoided). An average amendment requires 61 days and more than $450,000 to complete.[1,2]

Figure 2. Typical Site Recruitment Pattern

% of Sites	% of Evaluable Subjects Enrolled
20%	0%
30%	5%
20%	25%
30%	70%

Sources: Tufts CSDD, 2007; McKinsey & Company, 2004

Why Protocol Feasibility Assessments Fail

Common reasons protocol feasibility assessments fail include the following:

- The "Who"
  - The team that developed the protocol has unrealistic ideas about study implementation.
  - The team conducting the assessment does not include key players, such as "work horse" investigators, study coordinators, or specialists like radiologists and pharmacists.
  - The team conducting the assessment is not skilled in the assessment process itself or is consumed by other responsibilities.
- The "What"
  - The site questionnaire relies on checklists and yes/no questions, rather than questions that elicit more meaningful information.
  - The questions do not focus on the "red flag" issues that will most significantly determine success of the study, e.g., conflicts with standard of care, appeal to potential study subjects, and other practical aspects of study conduct.
  - Sites receive adequate information to conduct a meaningful analysis.
  - Data from sites is collected in ad hoc spreadsheets (but mostly stays on paper forms).
- The "Where"
  - Assessment teams do not personally visit research sites, thus relying on second-, third- or even fourth-hand information.

    - Assessment teams do not engage in face-to-face meetings in which facial expressions and body language can reveal unspoken issues.
    - Assessment teams have never personally visited the countries where a study is to be conducted.
- The "When"
    - The assessment timeline is artificially constrained by unrealistic dates for the investigator meeting, site initiations, and first subject visits.
    - Site questionnaires are distributed before essential information about the protocol is known.
    - Sites are given inadequate time to respond meaningfully to the questionnaire, favoring "quick and dirty" responses that give the sponsor the answers it wants to hear.
    - Sites are not given a starting date for the study, or the starting date is changed with the assumption that the site's interest and available resources will not change.
- The "How"
    - The assessment process is not thorough, consistent and systematic.
    - Sites are not held accountable for their contracted commitments on previous studies, much less their site questionnaires.
    - The assessment process is combined with site selection, yielding inaccurate information for both objectives.
    - The assessment team does not have thoughtful conversations with research sites to obtain meaningful feedback.
    - Investigators are approached with "interest queries," asking for their interest in conducting a study (based on very preliminary information), short-circuiting the already deficient site questionnaire process.
    - Site enrollment estimates are based on guesswork (or telling sponsors what they want to hear), instead of an evidence-based approach based on database review, chart review, or careful analysis of previous experience.
    - Feasibility assessments are not used as learning experiences to make the next assessment more accurate.
- The "Why"
    - Assessments are biased to justify decisions that have already been made.
    - Assessments are biased to support business development objectives (sites to sponsors/CROs and CROs to sponsors).

Fixing the Protocol Feasibility Assessment Process

Solutions to most of the above problems are obvious, although implementation may be challenging. The bigger question is whether the sponsor or CRO organization is really committed to an effective assessment process. The evidence suggests otherwise: assessment teams are often given unrealistic timelines, use tools they know to be ineffective, and follow inefficient processes they know prevent them from doing their work properly.

The best time to assess protocol feasibility is before the protocol is finalized and the site selection process begins. Investing in a proper assessment at the start pays big dividends later in both time and money. The key is to obtain a real-world assessment without paying the real-world price of midcourse delays and corrections during the study. Feasibility assessment is more than an opportunity to determine whether a study is, or is not, feasible. It is also an opportunity to make infeasible studies feasible and to make feasible studies even more successful.

Feedback from Sites

Sponsor/CRO assessment teams can provide a draft protocol or detailed synopsis, along with a draft budget, to a handful of sites of various types and across various regions to identify potential obstacles and opportunities. These sites should be selected based on their proven performance in conducting studies and also in providing information that is timely, accurate and useful. Many sites have effective feasibility assessment teams and processes of their own. In addition, sites might be willing to contact potential subjects and perhaps even conduct patient focus groups to evaluate interest and concerns.

Sites will be more willing to participate if their efforts result in booked studies and their feedback is seriously considered. Modest financial compensation for providing thoughtful feedback about the study design also may be appropriate.

Feedback can be obtained in written form and with market research techniques like structured interviews, operational advisory boards, and protocol optimization focus groups. Questions should be phrased to elicit recommendations that might increase the feasibility of the study.

Qualitative evaluation should be coupled with a quantitative analysis of the potential availability of the patient population. A detailed "recruitment funnel" analysis can reveal potential bottlenecks in contact, pre-screening, consent, screening and retention. These bottlenecks can be discussed with the sites for possible solutions. "Must have" site characteristics can also be identified. The resulting information can be used to modify the protocol and develop the project plan, especially for site selection, subject recruiting, and risk management. Any remaining significant challenges should be communicated to potential sites to avoid later surprises.

Site Feasibility Assessments

An effective site selection process asks the right questions, of the right individuals, in the right format, and at the right time.[3,4] Armed with a feasible study design, sponsors then can begin site selection. Site questionnaires can focus on"red flag" issues and "must have" site qualifications. Sponsors can also provide better information for the sites to use in their own feasibility assessments. The site questionnaire will still help sponsors select sites, but it will also help sites better select studies.

Additional fixes include:

- The "Who"
    - Design the questionnaire to obtain participation from key members of the study team. Ask the investigator, study coordinator, pharmacist, etc., to answer questions that pertain to their expertise.
    - Communicate (truthfully) to sites that they have been carefully pre-screened, so their participation in the study is relatively likely. This statement will encourage them to invest more time in evaluating the study.
- The "What"
    - Provide sites with adequate information to perform a thorough feasibility analysis, focusing on red flags, must-haves, and potential operational issues.
    - Include open-ended questions that help sites think through the issues, e.g., "Given the geriatric study population, how will you contact them about the study?" and "What, if anything, excites you about this study?"

- The "When"
  - Give sites adequate time to complete a thorough feasibility assessment, including an enrollment validation assessment. Two to three weeks should be adequate. Ask them to communicate their progress on a weekly basis.
  - Allow sites to request more time (and information) to complete a thorough analysis.
- The "How"
  - Avoid checklist questions. For example, instead of asking if the site has a bench-top centrifuge, ask for a copy of the maintenance log.
  - Consider compensating sites for conducting a database review/chart review assessment, and even contact a few likely subjects, to confirm enrollment potential.
  - Encourage sites to review previous, similar studies, especially comparing their feasibility assessments to their actual performance, and give the reasons for any shortfalls.
  - Encourage sites to "just say no" if the study is not a good fit, preferably with some explanation and suggestions.
  - Develop a tool to objectively score site responses. (See Figure 3.)
  - Train promising sites in how to conduct feasibility assessments to make better-informed study selection decisions.
  - Think beyond the questionnaire. Review past performance. Obtain references. Analyze databases. Converse with the sites. Organize focus groups.

Figure 3. Site Selection Scoring Tool Example

Factor	**Criteria**	**Site Scores**			
		A	**B**	**C**	**D**
Echocardiogram scheduling	Typically >3 days to schedule = 0 Typically 1-3 days to schedule = 1 Available same day = 2	2	0	1	0
Frequency of echocardiograms for most patients	Typically less often than annually = 0 Typically annually = 1	1	0	1	1
Searchable patient records	Paper charts only = 0 Billing codes for ICD-9s = 1 Electronic Medical Record = 2	2	0	1	2
IRB allows transport/ lodging reimbursement	No = 0 Yes = 1	1	0	1	1
[More factors]	[More criteria]				
Total score	>40 = probable high enroller 30-40 = probable moderate enroller <30 = probable low enroller	42	10	31	22

Source: © Customized Improvement Strategies, Inc.

Summary and Conclusions

With effective protocol- and site-level feasibility assessments, study sponsors can avoid infeasible studies and many protocol amendments, enhance research site performance, and ultimately conduct more successful studies. The key ingredient is a commitment to a thorough, consistent and systematic assessment process that accounts for real-world factors and supports process improvement from study to study.

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