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How Effective are Site Questionnaires in Predicting Site Performance?

By Sherry Reuter and Gretchen Esche

The use of site questionnaires in the site selection process is a time-consuming feature of almost every clinical research trial. Are they worth the effort, time and expense spent on them?

Lasagna observed that "Investigators overestimate, many fold, the pool of available patients who meet the inclusion criteria and would be willing to enroll in a particular trial." [1] Spilker discusses this phenomenon: "There 'always' seems to be one or more inclusion criteria that eliminate patients the investigator considered likely candidates. The investigator's optimism may reflect surreptitious behavior to obtain the clinical trial from a sponsor, or it may reflect inexperience or naiveté." [1]

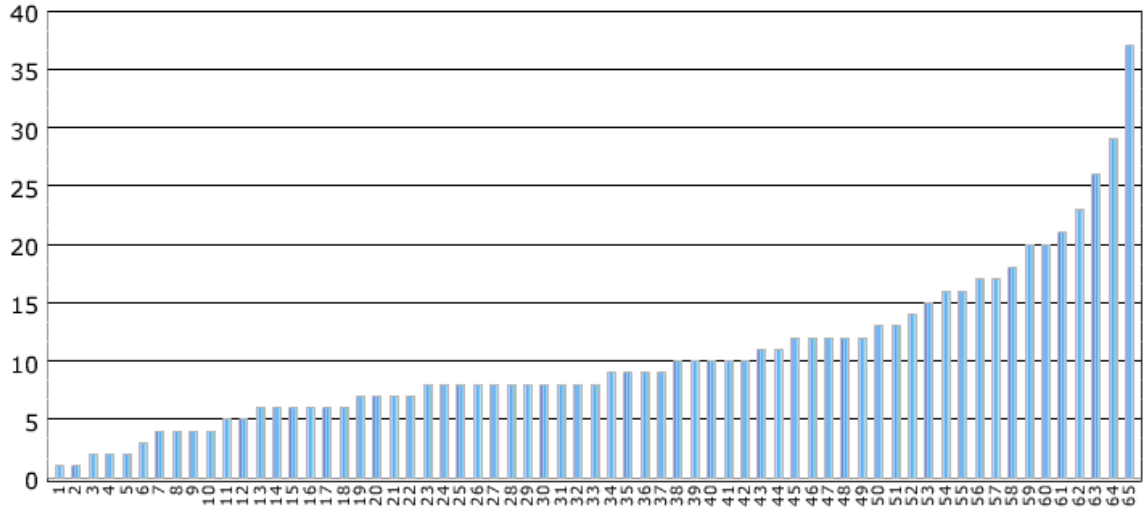
Herschel suggests that information returned on site questionnaires should not be taken as fact, as some sites are "overly optimistic" and will not accomplish what they state they can; others have "selective listening" and will try but fail; others are "grandiose" and say they can accomplish any goal; while others just do not truly understand the challenges of the trial.[2] Kibby estimates that "approximately one-third of selected sites perform ineffectively, another third perform marginally, and the upper third meet or exceed enrollment." [3] Identifying the ineffective sites that will enroll zero to two subjects would reduce the time and money wasted in clinical research tremendously.

Properly designed site questionnaires may address these issues. Therefore, a study was conducted to determine which questions, if any, are most useful in identifying sites that will successfully enroll subjects.[4] Statistical analysis reveals that none of the questions in the questionnaire studied had significant predictive value. However, the results of this research include data from only one clinical trial and therefore may not be generalizable.

Subject Enrollment

65 sites enrolled a total of 644 subjects in a Phase III rheumatoid arthritis clinical trial. A relatively high 66% of sites achieved the enrollment target of eight subjects per site. The median site enrolled 9 subjects, one more than the target. The top 13 sites (20%) enrolled 35% of the subjects. The bottom 40% of the sites enrolled 20% of the subjects. Of the 58 sites (89%) that predicted their enrollment in the questionnaire, 86% overestimated the number of subjects they would enroll.

Figure 1. Enrollment by Site



Results

Questionnaires completed by the 65 participating sites were analyzed to identify which of the 19 substantive questions were most predictive of subject enrollment. These 19 questions are commonly used on site questionnaires. The Chi-Square test of correlation was used to identify which questions were most significant in predicting whether or not the site reached its enrollment goal. With $p < 0.05$, a level of significance commonly used in clinical trials, there is only a 5% chance that the difference in enrollment occurred only by chance.

Table 1. Predictive Value of Questions
(Ordered from most to least predictive)

Question	p
Question F8. If you participated in an NSAID trial, how many patients could you enter into the trial each month?	0.057
Question B2. How many years of experience does your coordinator have?	0.096
Question F4. Are you agreeable with treating RA patients with a combination of low dose oral Corticosteroid and an NSAID?	0.159
Question F2b. If you and your site have participated in other trials to assess NSAID, how many?	0.359
Question F1b. If you and your site have participated in other RA trials, how many?	0.389
Question F3a. What percentage of your RA patients is treated with an NSAID other than COX-2 selective agents?	0.389
Question F6. How many (new to your practice) RA patients do you see a week?	0.401
Question F2e. Have you and your site participated in a clinical trial to assess NSAID treatment for RA in the past that	0.427

included a disease flare design?	
Question B3. How long has your coordinator worked for you?	0.496
Question B4. How many hours per week will the study coordinator have to work on this trial?	0.542
Question F5. How many RA patients do you typically see in a week?	0.566
Question F2a. Have you and your site participated in a clinical trial to assess NSAID treatment for RA in the past?	0.624
Question A4. Have you worked with the CRO in the last 12 months?	0.722
Question F7. Would you be interested in participating in a trial in which RA patients are withdrawn from their NSAID	0.755
Question F10. Are you participating in any trials that will conflict with this one?	0.762
Question A5. Have you worked with the Sponsor in the last 12 months?	0.978
Question A3. Have you acted as a PI or Sub I for any clinical study?	
Question F1a. Have you and your site participated in other clinical trials in RA?	
Question F9. Do you have/can you enroll patients that will be compliant with the protocol?	

None of the questions showed a statistically significant ($p < 0.05$) association between the information the sites provided and their actual enrollment performance. However, there is a 94% likelihood that Question F8 has predictive value, a 90% likelihood that Question B2 has predictive value, and an 84% likelihood that Question F4 has predictive value. The other questions have substantially lower likelihoods of predictive value. Questions A3, F1a and F9, the last three listed in the table, could not be evaluated because all participating sites answered them "yes."

Future Research

Additional research could determine whether modifying the questions will improve their predictive value. For example, it would be interesting to compare the question "Are you participating in any trials that will conflict with this one?" with the questions "Do you expect to be conducting any competing trials in three to six months? If so, how will you allocate subjects and staff time between the studies?" Other methods of statistical analysis may enable study sponsors to reliably identify the most promising sites. Pattern recognition, for example, can identify a meaningful combination of answers. It may also be possible to identify questions that flag Herschel's failure modes (above). It may be useful to analyze site questionnaires in conjunction with electronic medical records and databases of patient populations and physician prescribing patterns maintained by managed care organizations, insurance companies, and market research firms.[5]

There is clearly room for improvement in site questionnaire forms. With systematic testing during the course of clinical trials, the cost for substantial improvements in site selection could be very small and the benefit very large.

References

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