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Screen Failures in Clinical Trials: Financial Roulette or the Cost of Doing Business?

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The financial impact of screen failures in clinical trials is determined by two factors: cost per failure and probability of occurrence. If the cost of a failure is nominal, then the burden of even high-probability events may be negligible. However, if the cost of a failure is high, then even a low probability of failure may give pause, and the question of who pays for screen failures –sponsor or investigative site – becomes very important. Sites naturally want the sponsor to pay because the site is doing the work. However, sponsors are naturally concerned that paying sites regardless of success will encourage sites to screen unlikely subjects just to earn the screening fee.

Screen Failure Scenario

A sponsor offers a trial to a site with revenue of $3,000 and profit of $1,000 (33%) per completed subject. However, the trial is expected to have a screen failure rate (SFR) of 80%. That is, if the site screens five potential subjects, only one (20%) is expected to qualify for the study.

The clinical trial agreement states that the sponsor will pay the cost of $400 per screening, including up to four screen failures per enrolled subject. In other words, if one of the first five subjects enrolls in the study, the sponsor will also pay for four screen failures, a total of $2,000. However, if none of the first five subjects enrolls, the sponsor will pay for none of the screen failures.

There is an 80% chance that the first subject will fail the screen, and a 64% (0.8 X 0.8) chance that both of the first two subjects will fail. Continuing the calculation shows that there is a 33.8% (0.8^5) chance that all of the first five potential subjects will fail the screen. In this case, the sponsor pays nothing and the site loses $2,000 on the study. The site may try to recoup its losses by continuing to screen potential subjects. However, each additional screening has only a 20% chance of recovery, plus it incurs the cost of the additional screening, which will not be recovered. In other words, the likely payoff for continuing to screen does not improve.

It is, of course, possible that a site will enroll more than one subject out of the first five. Table 1 shows the likely financial impact for all possible outcomes. There is a 33.8% chance that the site will enroll zero subjects, costing it $2,000 in screening costs with no offsetting revenue. There is a 41% chance that it will enroll one of five subjects, generating a profit of $1,000. The chances of enrolling two, three, four or five subjects are 20.5%, 5.1%, 0.64% and 0.3% respectively. On average, then, a site might expect to earn $345 (11% of $3,000 expected revenue) on this trial because the 33.8% chance of losing $2,000 is offset by the 64.2% chance of earning a profit. The terms of the screen failure payment thus reduce the expected profit margin from 33% to 11%.

If 100 sites in an 80% SFR study each screen five potential subjects, about 34 of the sites will enroll zero subjects. Suppose the sponsor had agreed to pay for every screen failure, regardless of success. In this scenario, the study sponsor may conclude that 34 of the sites exploited the payment scheme by screening potential subjects who were unlikely to enroll; it is unlikely to trust those sites in the future.

Table 1. Financial Impact ($) of SFR = 0.8 with 5 Screens

Enrolled Subjects	Probability	Screening Costs	Screening Payment	Expected Screening Payment	Revenue (Post-Screening)	Expected Revenue (Post-Screening)	Gross Profit (Post-Screening)	Net Profit	Expected Net Profit
0	32.77%	2,000	0	0	0	0	0	-2,000	-655
1	40.96%	2,000	2,000	819	3,000	1,229	1,000	1,000	410
2	20.48%	2,000	2,000	410	6,000	1,229	2,000	2,000	410
3	5.12%	2,000	2,000	102	9,000	461	3,000	3,000	154
4	0.64%	2,000	2,000	13	12,000	77	4,000	4,000	26
5	0.03%	2,000	2,000	1	15,000	5	5,000	5,000	2
Total	100.00%			1,345		3,000			345

Assumptions: Five subjects are screened; $3,000 revenue per enrolled subject; $1,000 profit for an enrolled subject; cost of screening is $400 per subject; screening payment is treated as non-revenue reimbursement; gross profit is profit after screening cost and payment; net profit is gross profit minus screening cost plus screening payment; no screening payment unless at least one out of five subjects enrolls; expected revenue and profit consider the probability of enrolling each number of subjects.

Possible Solutions

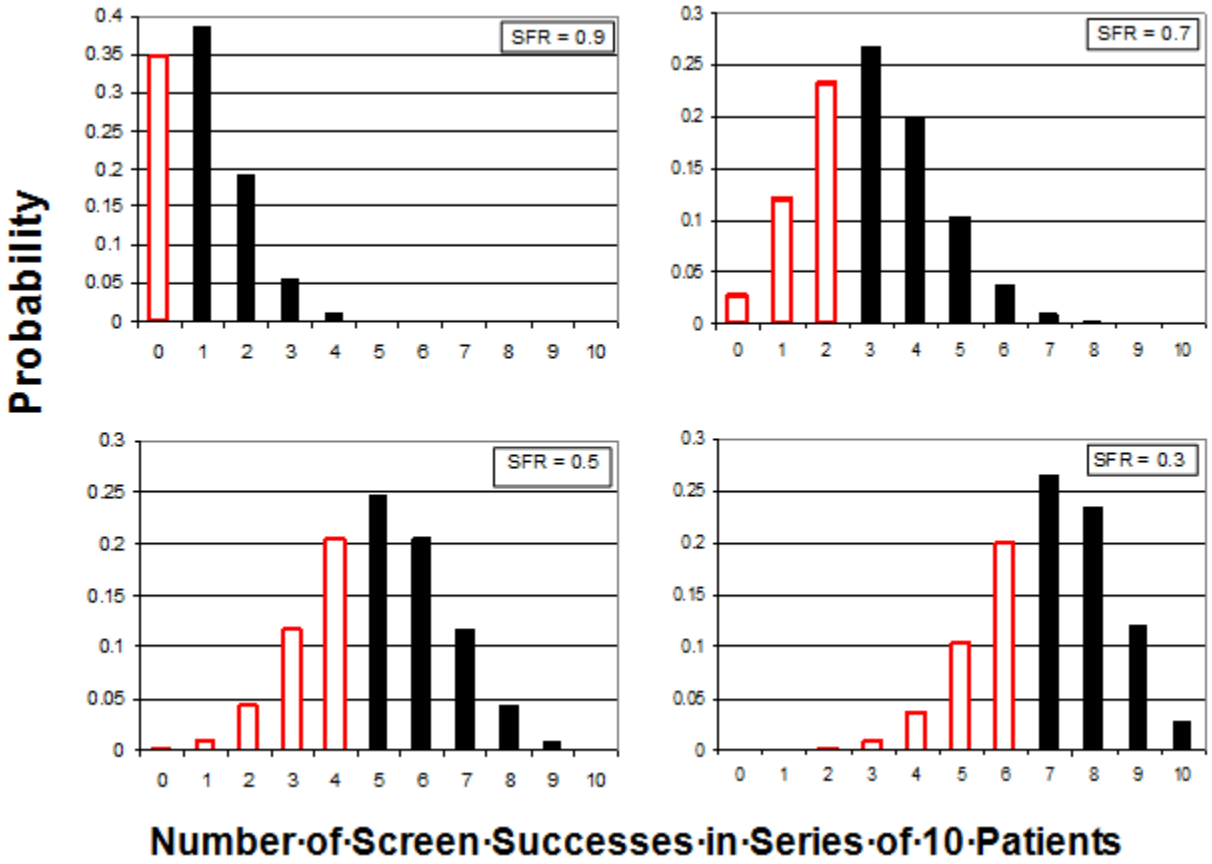
Is there a screen failure payment system that reconciles the conflicting perspectives of the sites and sponsors? The sponsor has two options:

- **Share the risk with the site.** In this scenario, the sponsor pays the site a partial fee for each screen failure. For example, the payment might compensate the site for the cost of the screenings, with no profit margin (making the big assumption that the site operates at a profit). The site would then have no financial incentive to screen unlikely subjects. The cost could be calculated on a fully allocated basis, including overhead, or on a variable cost basis, covering only direct, variable costs (which can be calculated in a variety of ways). Because the site's risk is reduced, it should be willing to accept a lower profit margin on enrolled subjects, offsetting the increased cost of the screen failures. Sites should also be willing to screen more potential subjects before giving up and cutting their losses.
- **Reward the site for taking the risk.** In this scenario, the sponsor increases the screen failure payment, for example to 150% of normal. Over the course of three trials, the site will probably lose money on one of the trials, but make enough on the other two to cover the losses, with a bit extra for taking the risk. However, this approach has three serious drawbacks: First, it may take many trials for the numbers to work out; second, most investigators do not conduct enough trials to see the numbers work out; and third, this payment scheme creates enrollment incentives that are ethically unacceptable.

Study sponsors are thus left with only one feasible option: partial payment to sites for every screen failure. Any other screen failure payment scheme generates significant losses for 25-

35% of the sites on a given study, and creates suspicion and ill will between sponsors and sites. Of course, sponsors could choose to work with sites that do not understand the gamble they are taking and go out of business sooner or later.

Figure 1. Probability of 0 to 10 Screen Successes in a Series of 10 Patients for Different Values of Screen Failure Rate (SFR)*



* Open bars represent conditions in which the site does not recover all expenses for screen failures. Graphs were generated using the BINOMDIST function in MS Excel.

Other Screen Failure Rates

Figure 1 shows outcomes of trials with different SFRs in which 10 candidates are screened. As SFR decreases from 0.9 to 0.3, the probability of the worst case (0 out of 10) decreases. However, if the sponsor's stringent condition of no payment until a site has a screen success holds, then moderate success rates can still result in a financial loss to the site. Thus, if SFR=30% (3 out of 10), then the sponsor will pay for 10 screens if the site enrolls seven subjects. Thus, a site that enrolls up to six patients out of a series of 10 candidates will not recover all screening expenses. The message is clear: There is a high probability of not recovering expenses when screen failure rates are greater than 10%, and accepting contract terms that condition reimbursement on a set number of screen successes is a risky proposition.

Low Screen Failure Rates

In many trials, the SFR is expected to be low (e.g., <10%), and sponsors may decline to pay for screen failures. In these situations, sponsors are passing the cost of screen failures

to the sites. Sites must consider the expected cost of screen failures as a "cost of doing business" and factor this cost into their pricing structures. With an SFR of 10%, a site can expect, on average, that one of 10 patients will screen-fail. A site can protect its expected profit margin by spreading the cost of the screen failures over the cost of enrolled subjects. For example, with SFR=10%, nine enrolled subjects must cover the cost of one screen failure. If the screening cost is $400 per subject, the price for each enrolled subject must thus increase by $44 ($400/9) to cover the one expected screen failure.

However, the issue is not just cost; it is also risk. If SFR=10%, there is a 26% chance that more than one patient will screen-fail. In addition, the true screen failure rate may be higher than 10%. The $44 pricing premium does not include a "risk premium" that compensates the site for taking these risks.

Discussion

Screen-failure terms in clinical trial agreements can impose significant financial risks on the site. Site managers who might be tempted by prospects of big profits for the successes should ask what is the worst that can happen, how likely it is, and if it is worth the gamble. The examples above are only illustrative, but suggest that a smell-test should usually be sufficient.

Many institutions have policies that discourage accepting recruitment bonuses because they may induce investigators to recruit subjects inappropriately. Trials with high SFRs impose a recruitment penalty that may be no less of an ethical challenge. It can be very difficult to resist the pressure to enroll at least one subject as the screen failures spill red ink. In contrast, the cost-of-doing-business argument might be valid when the anticipated SFR is very low, but in the absence of data about the SFR, assuming the risk can be a bad bet.

Note

The probability of not having a screen failure is given by the MS Excel function BINOMDIST(s, n, 1-SFR, FALSE), where s is the number of screen successes, n is the number of patients screened, and SFR is the screen failure rate.

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