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Site Contracting and IRB Review Processes: Parallel or Serial?

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After a study sponsor invites a research site to participate in a study and the site accepts the invitation, the site has two primary tasks: to obtain approval from the IRB and to negotiate the clinical trial agreement (CTA), including the budget. The site can tackle both tasks in parallel or it can tackle them serially, one and then the other. (It can also negotiate the budget in combination with, in parallel with, or serially to the rest of the contract.) Both tasks must be completed before the sponsor can initiate the site.

In most cases, the site can get to initiation faster and start enrolling study participants sooner with the parallel approach. On the other hand, if it fails to complete either task, it will have wasted time and effort on the other task. For example, if the parties are unable to agree on a budget, the time spent preparing the regulatory package for the IRB will have been wasted.

For many sites, the best approach is obvious. For example, if a site is always able to negotiate a CTA with a particular sponsor, there is no point waiting to prepare the regulatory package. Similarly, if a sponsor is likely to insist on unreasonable contract terms, but obtaining approval from a central IRB is quick and easy, it is best to wait to prepare the regulatory package until the CTA's prospects become clear.

Figure 1 shows what to do when, depending on the combination of fast vs. slow, cheap vs. expensive, and low risk vs. high risk for both processes. The primary rule used in this scheme is to complete both processes as quickly as possible but in a reasonably economical manner. For example, a fast, cheap, high-risk process should be completed before a fast, expensive, high-risk process, so the expensive process can be avoided if unnecessary. In contrast, a fast, cheap, low-risk process should be pursued in parallel with a slow, expensive, high-risk process so the combined process doesn't take even longer. If both processes are fast, expensive and high-risk, one should be completed before the other. In contrast, if both are slow, expensive and high-risk, a parallel process is appropriate,

Figure 1. Scenarios for Parallel vs. Serial Processes

		IRB Approval							
		FCL	**FCH**	**FEL**	**FEH**	**SCL**	**SCH**	**SEL**	**SEH**
CTA Negotiation	**FCL**	par	IRB	CTA	CTA	par	par	CTA	CTA
	FCH	CTA	par	CTA	CTA	par	par	CTA	CTA
	FEL	IRB	IRB	par	IRB	par	par	CTA	CTA
	FEH	IRB	IRB	CTA	either	par	par	CTA	CTA
	SCL	par	par	par	par	par	par	par	par
	SCH	par	par	par	par	par	par	par	par
	SEL	IRB	IRB	IRB	IRB	par	par	par	par
	SEH	IRB	IRB	IRB	IRB	par	par	par	par

Fast vs. Slow Cheap vs. Expensive Low Risk vs. High Risk
CTA = CTA negotiation first IRB = IRB approval first
para = parallel either = either first

assuming the site is very interested in that study. Different sites will have different ideas about, for example, how long a process has to take to qualify as fast or slow. In addition, Figure 1 does not consider intermediate values.

Figure 1 assumes that the study can initiate at the site as soon as these two processes are complete. However, if that is not the case, the analysis changes. For example, if there is a 12-week window before the site can initiate the study and each process takes four weeks, there is plenty of time to complete them sequentially.

Figure 1 does not allow the second process to start midway through the first process. However, doing so might make sense, for example, if the risk that the first process will succeed is largely eliminated during the early part of that process. Similarly, costs might be incurred unevenly during a process. For example, if the costs of the second process are incurred mostly in the middle of the process, it might make sense to start that process early and then pause it, if appropriate, before the major costs are incurred.

Mathematical Comparison of the Two Approaches

The site can compare projected earnings from the parallel vs. serial approaches mathematically, using estimated values:

Serial process: Expected earnings equals probability both processes complete times net earnings, minus cost for both processes

Es = (Pn X Pi) X (Em – (Lw X (IF(Tn+Ti-Ts<0,0,Tn+Ti-Ts)))) – ((1-Pn) X Cn) – (Pn X (Cn + Ci))

Parallel process: Expected earnings equals probability both processes complete times net earnings, minus cost for both processes

Ep = (Pn X Pi) X (Em – (IF(MAX(Tn,Ti)-Ts<0,0,MAX(Tn,Ti)-Ts) X Lw) – (Cn + Ci)

where:

Es = Earnings from study with serial approach

Ep = Earnings from study with parallel approach

Em = Maximum potential earnings (contribution to margin)

Lw = Lost profit per week of delay (based on lost enrollment)

Cn = Cost of negotiating a CTA (including salaries)

Ci = Cost of obtaining IRB approval (including salaries)

Pn = Probability of negotiating a contract

Pi = Probability of obtaining IRB approval

Tn = Time required to negotiate a contract (weeks)

Ti = Time required to obtain IRB approval (weeks)

Ts = Time before study can start (weeks)

assuming:

For the serial approach, CTA negotiation is the first process.

The cost of a process is independent of whether it completes or not. (Unsuccessful processes can consume more resources than successful processes.)

No other site costs are incurred while these processes are underway.

Enrollment during the study is at a constant rate.

There is no risk that the sponsor will withdraw the invitation based on slow processes. (This is a big assumption.)

The challenge is in estimating the values for the variables, but accurate estimates are worthwhile because these values are also very useful for managing the processes and pricing services. Figure 2 shows some example scenarios based on various parameter values:

Figure 2. Example Scenarios

	A	B	C	D	E	F
Em	20,000	20,000	20,000	20,000	20,000	20,000
Lw	2,000	2,000	2,000	2,000	2,000	500
Cn	1,600	1,600	1,600	1,600	4,000	1,600
Ci	2,500	2,500	1,000	2,500	2,500	2,500
Pn	0.8	0.6	0.8	0.5	0.5	0.6
Pi	0.9	0.9	1.0	0.8	0.9	1.0
Tn	4	4	4	4	4	2
Ti	8	8	1	8	8	2
Ts	6	6	2	6	6	4
Es	2,160	1,220	8,800	350	-1,650	8,900
Ep	7,420	4,540	10,200	2,300	700	8,500

Scenario A is the baseline. Red = change from baseline

A Microsoft Excel calculator is at
http://www.firstclinical.com/journal/2015/1502_Parallel.xls.

Considerations

A serial process reduces potential earnings if the study ends before the site can reach its enrollment goal (which might have been reduced by the sponsor already, based on a late start). It might also prevent the site from participating in the study at all. This factor helps explain why smaller research sites with quick processes have taken market share from larger sites with lengthy processes. Even worse, slow processes might prevent that sponsor or CRO from inviting the site to participate in future studies that can enroll quickly at other sites, or any studies at all. Given how often sponsor and CRO clinical research personnel move from company to company, it does not take long for the speed of a site's processes to become known throughout the industry.

While the analysis above assumes that processes take exact lengths of time, there can be substantial uncertainty for a specific study. Depending on its risk tolerance, a site can estimate project timelines based on the historical median average or a metric like "the time period required for an 80% probability that the process will complete within that time period." This same uncertainty means that a site might want to revise its plan part way through. For example, if the first process in a serial process is taking longer than expected, it might want to start the second process before the first one completes.

The budget is often negotiated separately from the rest of the contract. At some sites, sponsors and CROs, different people conduct the two negotiations. In this case, the parallel

vs. serial question also arises within the contract negotiation process. If IRB approval will be quick and a successful CTA negotiation is likely, parallel budget and contract negotiations make sense. If IRB approval will be slow, both can wait. If the budget, for example, is more likely to be problematic than the rest of the CTA, the site should negotiate the budget before the contract.

The CTA can be signed before IRB approval, provided it states that the contract is valid only with IRB approval.

The above analysis ignores any resource constraints and other start-up activities.

The above analysis considers the options from the perspective of the site's direct profitability. However, we can also look at them from the sponsor's or CRO's — i.e., the customer's — perspective. In most cases, customers prefer the parallel approach, so the site can start enrolling participants sooner. Taking the risk of a parallel process is thus good customer service, assuming the experience does not discourage the customer from taking its own risk for future studies. If the site feels uneasy taking the risk, the sponsor might be willing to write a letter to the site agreeing to reimburse the site for its costs, even if the site does not conduct the study. This option is more likely if the sponsor really wants the site to participate in the study and the source of the risk is identifiable, e.g., IRB approval is uncertain.

Another perspective is that of the investigator and research personnel. Since they are usually anxious to get started on a study, the parallel approach is superior. However, if the site is unable to negotiate a CTA, they prefer not to waste time preparing the regulatory package.

The CTA negotiation process involves both the site and sponsor/CRO. The same is usually true for the IRB approval process, but much less so. As a result, the site has less control over CTA timelines, so the additional uncertainty should be factored into the equation. There is also the chance that a study will not launch on schedule, so expending resources to accelerate the site's start-up processes could be wasted.

Master CTAs and master chargemasters reduce the cost, time and risk of negotiating CTAs. If IRB approval will be quick and easy, as well, both processes can be completed in parallel. If IRB approval will be slow, it's still worth completing the CTA expeditiously, for two reasons: First, it demonstrates the site's interest in the study. Second, it makes it harder for the sponsor to withdraw its invitation for the site to participate in the study.

Some coordination is required between the contract and regulatory processes. Some terms in the CTA, e.g., the stipend plan, overlap with terms in the informed consent form. The IRB might place conditions on the site that, for example, increase the cost of enrolling participants or using their biosamples. If the CTA and regulatory processes are conducted in parallel, these issues can be resolved during the processes. If the processes are pursued serially, the second process has the advantage of seeing the end result of the first process, but it might require restarting the first process to address any inconsistencies.

One way to answer the parallel vs. serial question is to reduce the risk of failing to negotiate a contract or obtain IRB approval to essentially zero. If these risks are very small, a parallel process is clearly preferable. However, reducing the risk too much can have a negative impact on profitability because it requires limiting relationships to only proven sponsors and CROs, accepting only the most appealing studies, and negotiating budgets in a very accommodating manner. In addition, if a site always comes to agreement with sponsors, it won't learn what they are actually unwilling to accept.

Accelerating the Process

The above discussion assumes that process durations are fixed. This assumption is probably not correct unless a site's processes are already among the fastest in the industry. Rather than optimizing the order of the start-up processes, research sites can try to accelerate the processes, especially the longest ones. Study sponsors much prefer working with research sites with rapid start-up processes, so it is worthwhile to determine why processes are slow and accelerate them where possible. Even if a sponsor is willing to contract with a site that starts up slowly, the enrollment window will be shorter, so the opportunity for a successful study will be limited.

There are six common reasons for slow start-up processes:

- **Low management priority.** Site management simply may not care that much about rapid start-up processes. After all, clinical research is only a tiny fraction of the activity at many sites that conduct clinical research. However, if clinical research is worth doing, it is worth doing well, so it is incumbent on management to decide whether it is worth doing and, if the answer is "yes," do it well. A small investment in process improvement can pay large returns.
- **Institutional policy and "that's the way we've always done it."** Monthly IRB meetings are inherently slow for most studies, and also make process duration unpredictable. Research sites can, instead, hold short, weekly IRB meetings or contract with an independent IRB. A significant rate of IRB non-approvals suggests that better pre-review of applications by IRB administrative staff would be worthwhile.
- **Mistaken priorities.** A research site might be able to increase a study budget with an additional month of negotiation, but will the additional revenue offset the cost of the negotiation and, more importantly, the loss of revenue from a shorter enrollment period? Will that study sponsor invite the site to conduct its next study, the one that will enroll quickly (and profitably)?
- **Lack of resources.** Requiring legal review of all contracts, when legal resources are limited, creates a bottleneck. With training and detailed instructions, non-lawyers can handle many CTA negotiations, or at least limit the questions that need legal review. Master CTAs largely eliminate the CTA negotiation process.
- **Internal focus.** Research sites should expand their focus beyond their internal processes to also include the study sponsor's processes. Sites should understand the study sponsor's timelines and bottlenecks. If, based on prior experience, the site knows that a particular CTA term will be problematic, it can raise that issue early in the process.
- **Lack of process management.** Research sites should know how long their processes take, and not just the averages. If a process is usually, but not always, fast, it might be worthwhile to start the process sooner. Sites should know the critical path (i.e., the longest path through the process). They should know where the bottlenecks are and how to prioritize specific studies through them. When study coordinators are multitasking, their priorities may not match those of site management.

The above discussion also assumes that the probability of successfully completing start-up processes is fixed. While fast processes are almost always better than slow processes, it is not necessarily desirable for every study to successfully gain IRB approval and generate a signed CTA. As an analogy, most salesmen do not pursue only the leads that are guaranteed to result in successful sales. Pre-screening studies for the likelihood of successfully navigating the process can avoid wasted effort, but it can also create an overly

conservative culture that misses good opportunities. Management should tune processes to generate a target failure rate, preferably with failures that are not prohibitively costly.

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