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Accelerating the Process of Negotiating Clinical Trial Agreements

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Successful clinical trials require the timely completion of numerous business processes. In one key process, the study sponsor negotiates a clinical trial agreement (CTA) with each research site. CTA negotiation (including the budget) is the most common cause of study delays.[1] These delays not only slow clinical research, they also shift it to sites that complete the process relatively quickly. The relatively slow performance of academic sites (sites that use local IRBs) –an average of 133 days vs. 40 days for non-academic sites (sites that use central IRBs)[2] – helps explain why their market share in the U.S. has declined from about 80% to 26% over the 15 years from 1991 to 2006.[3] Clearly, sponsors and sites with relatively efficient processes have a significant advantage over their competitors.

CTA negotiation is a business process. Like any other business process, it can be improved with Six Sigma, total quality management, and other management methods. These methods take various approaches to answering the same question: "How can we improve the time, cost, quality and reliability of the process?" This article examines the CTA negotiation process and identifies opportunities for improvement that any sponsor, site, contract research organization (CRO), or site management organization (SMO) can implement.

Figure 1. True Story

When I was running a site, I negotiated a CTA with a large pharmaceutical company. Despite multiple requests, I couldn't get signature copies. Supposedly, they had been mailed. I finally tracked down the person who owned the file cabinets where the physical CTAs were stored. She looked in our file and found the signed CTA. I hadn't signed, it, so who had? It turned out that they had mailed it to another site, which signed and returned it. The net result was a three-week delay before we could start enrolling.

This article's focus is on time reduction, but it applies equally well to cost, quality and reliability. As Figure 1 illustrates, all four dimensions are often closely related, with improvements in one automatically generating improvements in the others.

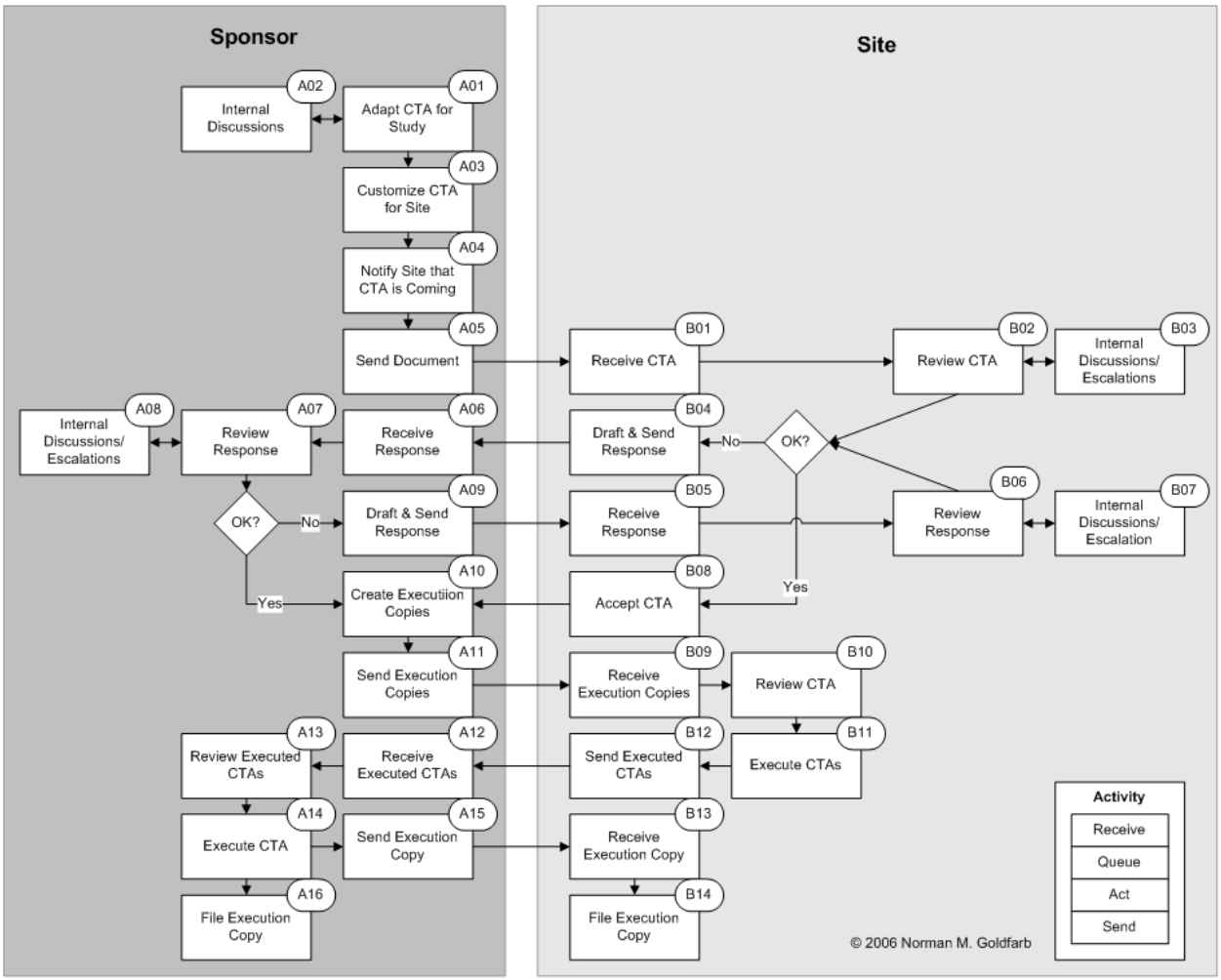
CTA negotiation is, by definition, a cross-organizational process. Improving the internal process of one party to the negotiation has limited benefit if the other party's process remains slow. This limitation can be addressed by improving the process in ways that speed it up for one's partners. For example, clear, well-formatted language in a sponsor CTA template speeds the review process at the site. A cogent explanation can be prepared in advance of why some terms (e.g., indemnification by a state university) are non-negotiable. The limitation can also be addressed by involving business partners in the improvement process. Master CTAs, as described below, are an example of this approach.

Figure 2 describes the typical CTA process in a flowchart with a moderate level of detail. The process crosses back and forth between the sponsor and site. Assuming none of the steps – except negotiation – are skipped, the shortest path through the flowchart involves 19 steps. Because each step in the process is a potential source of problems, each requires attention. Some obviously cause more problems than others, but the problematic steps vary from organization to organization. For example, the process in a large organization may involve multiple approvals, while the process in a small organization may be blocked if a single key individual is on vacation.

Every step in the process has four components:

- **Receive.** The document (or email or etc.) arrives for processing.
- **Queue.** The document waits its turn.
- **Act.** The required processing occurs.
- **Send.** The document is sent to the next step.

Figure 2. CTA Negotiation Process



Each of these steps is prone to common problems, such as:

- **Receive.** The document may go to the wrong person. It may get misfiled. The recipient may not be there when it arrives.
- **Queue.** There may be a large number of other documents in the queue. It may sit while other higher-priority or easier-to-handle documents are processed.
- **Act.** The process may be time-consuming or require multiple sub-steps. The responsible person may be inexperienced and therefore work slowly or make mistakes. He/she may require assistance, guidance or authorization from someone else who is not available.
- **Send.** The document sits in the out-basket or a stack of other papers. The wrong version goes out. It goes to the wrong person.

Statistics

Business process improvement methods often include math-heavy statistics. However, non-statisticians can achieve significant improvements with simple metrics (quantitative measurements), slicing and dicing the data, and calculating percentages. Straightforward questions can identify problems areas and track improvements:

- How long does it take to negotiate each CTA?
- What is the average time?
- What percentage of CTAs takes longer than the target time?
- How long does each major step in the process take on average?
- Do certain types of CTAs take longer than other types?

Although business process improvement does not require complex statistics, it is helpful to understand one statistical aspect of business processes: their graphical shape. With this picture in mind, improving a business process becomes an exercise in moving the shape around.

Many business processes can be described with a symmetrical "normal" (bell-shaped) curve. For example, the time required for a bank teller to process a deposit transaction may be three minutes plus-or-minus one minute 95% of the time. For example, the waiting time in the queue to get to the bank teller may average five minutes, with a short tail on the left (first customer of the day) and a long tail on the right (lunch-time customers). Other business processes are best described with irregularly shaped curves. For example, if there are two bank tellers, one may be faster than the other, creating a "bimodal" distribution. In some cases, an irregularly-shaped curve indicates the presence of two difference processes. For example, cash deposits may take longer on average than check deposits because the teller has to count the cash. As note above, CTA negotiations consist of numerous steps, each of which is a sub-process.

The CTA negotiation process in many organizations can benefit from two kinds of improvement:

- The process takes too long on average.
- The process takes way too long for some negotiations.

We will now discuss how several process improvement methodologies can help address these problems.

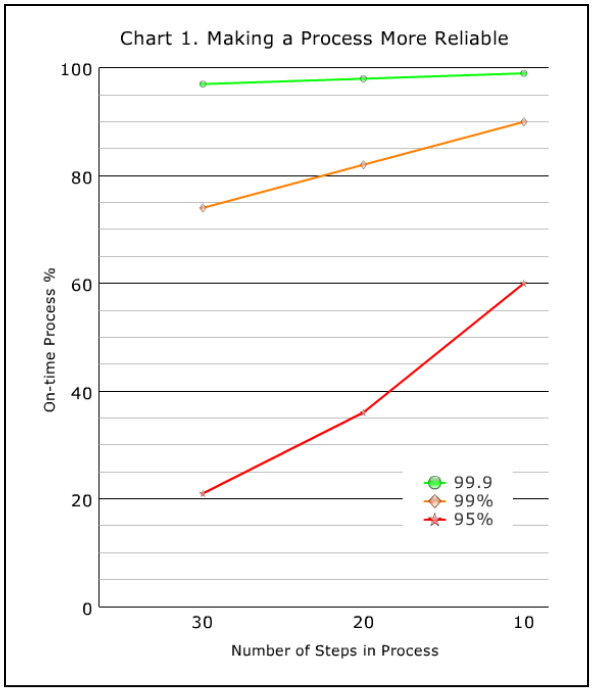
Six Sigma

The term "six sigma" refers to six standard deviations in a normal distribution. In a six sigma process, each step generates successful results 0.9999997% of the time and fails only once in 3.5 million tries. When the error rates of all the steps in the process are multiplied together, the error rate in the end-product should still be acceptable.

The six sigma goal is arbitrary; in practice, the goal is to improve quality (including delivery) to the level that, for practical purposes, errors can be ignored. In a complex product such as an automobile with thousands of parts and millions of process steps, even six sigma quality at each step may not be good enough to deliver end-products with an undetectable level of defects.

Negotiating a CTA is much simpler process than building an automobile, but Six Sigma principles still apply. With the 30-step CTA negotiation process in the diagram above and a 1-sigma (95%) quality level at each step, the chance of completing a negotiation on time is $(0.95)^{30}$, or only 21%. As shown in Chart 1, increasing the success rate for each step to

99% and decreasing the number of steps to 10 increases the probability of on-time completion to 90%, still not a very reliable process.



According to Six Sigma theory, there are three main steps to improving a business process:

1. **Measure process performance**. Measure in detail –and keep measuring it – to identify problem areas and monitor improvements. For example, there may be too many CTAs in queue or obtaining management signatures may be bottleneck.
2. **Control variability**. If the process has an acceptable average time to completion but a high range of completion times, the underlying source of the problems may not be addressed, improvements may be temporary, and inconsistent results may require disruptive firefighting. For example, if the time through the negotiation process ranges from one to twelve months, the Six Sigma priority is to reduce the range to, for example, one to three months. Pulling in the long tail probably will also reduce average processing time as a side benefit.
3. **Move the mean average.** Once the process is under control, attention can be directed to the "low-hanging fruit" – the steps where improvement is easiest. Incremental improvements bring the mean average to an acceptable level. For example, CTA negotiations often cover the same ground. By preparing clear negotiation arguments in advance, copying-and-pasting replaces reinventing the wheel for each negotiation.

Figure 3. Six Sigma Steps

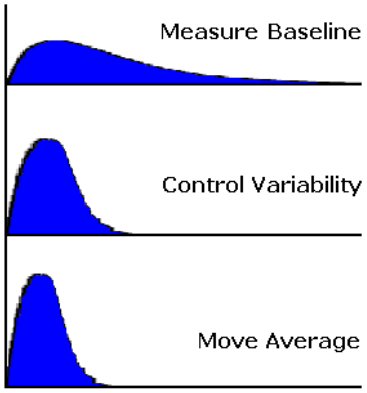


Figure 3 describes these three steps graphically.

Once a process meets requirements, the priority shifts from improving performance to maintaining performance, although incremental improvements should still continue. (See Statistical Process Control and Total Quality Management below.)

Total Quality Management (TQM)

Total quality management, as exemplified by "The Toyota System," has demonstrated that quality is not only free; it substantially increases profits. Among many other benefits, delivering high-quality products and services eliminates rework, an extremely expensive and wasteful process. One key insight of The Toyota systems is that it is far cheaper to build quality in rather than inspect errors out. The entire process becomes simpler and faster when each step in the process can rely on high-quality input from the previous step. For example, if there are no defects, there is no need for inspections.

TQM emphasizes a continuous flow of incremental improvements from the bottom of the organization's hierarchy – the people who do the hands-on work. Quality is not an on/off

switch; improvement derives from a multitude of small steps forward. Each improvement improves quality and also exposes opportunities for the next batch of improvements.

CTA negotiation can be viewed as 100% inspection and rework. The whole process is designed to correct deficiencies in the initial CTA template. Imagine a negotiation process in which the initial template is acceptable to both parties – there is no negotiation. Such processes exist today; they are called "master clinical trial agreements."[4]

Master clinical trial agreements are practical when a site conducts a high volume of trials for a sponsor. However, with a low volume of transactions, the sponsor can still minimize the inspection and rework steps in CTA negotiations in three ways:

- Write CTA templates in clear, straightforward language.
- Start in the middle, e.g., leave out the sponsor-friendly terms that experienced sites will not accept but require reinventing the wheel time and time again.
- Use widely accepted model agreement language, e.g., MAGI's Model Clinical Trial Agreement.[5] MAGI's Model CTA includes sponsor-friendly, site-friendly and neutral multiple-choice language. Sponsors can use sponsor-friendly language, but the deciphering and "gotcha"-hunting task for sites is minimized.

Statistical Process Control (SPC)

Statistical Process Control refers to systems that closely monitor the performance of a process to detect and correct discrepancies as quickly as possible. Efficient and reliable pharmaceutical, biotech and medical device manufacturing processes employ statistical process control. The statistics are used to sift through the random events in any normal process to identify significant detrimental changes in the underlying process. For example, it may be acceptable for the length of a machined part to vary by +/- 0.1 inch, but if the average length increases by 0.01 inches, the underlying process has changed and needs to be brought back under control. The statistics can be, but need not be very sophisticated to be useful.

CTA negotiation, like any business process, can be likened to a manufacturing process, in this case, manufacturing a signed CTA from a CTA template.

For example, if the Vice President of Research has agreed to sign and return CTAs in two days plus or minus one day, and the latest one has not been returned by the end of the third day, that step of the process is out of specification and intervention is called for. Intervention may take the form of a mechanical analogy such as tightening the screws or turning up the heat, but it could also mean a quick call to the VP's office that discovers a vacation to be the cause. This process discrepancy feeds into the TQM program for incremental improvement. Perhaps a back-up signer can be identified or the need for the signature dispensed with entirely.

Statistical Process Control is a key element of Six Sigma.

Risk-based Management (RBM)

Risk-based management refers to the application of management resources to the parts of a process that pose the greatest risk, in terms of likelihood and negative ramifications. Very few processes operate 100% correctly. Unless an organization has unlimited resources, it has to apply those resources to the most likeliest problems. The challenge is to identify most significant risks and then develop programs to avoid or mitigate them.

FDA has adopted a risk-based strategy for inspecting pharmaceutical manufacturing facilities for cGMP (current Good Manufacturing Practices) compliance. It is applying the

strategy more to research site inspections.[6] Of course, high-enrolling sites in pivotal studies have always received more than their share of FDA visits.

In a CTA negotiation process, some steps are more likely to cause problems than others. The chance of a problem in other steps may be lower, but problems that do occur are more costly. Some steps have both properties, and therefore deserve priority attention. For example, if a key step, e.g., legal review, is performed by a single person who has other important responsibilities, major delays may occur frequently. Management should invest the resources to establish an early warning system his step so corrective action can be taken immediately. It should also invest in ways to avoid or mitigate the risk. For example, the frequency of occurrence can be reduced (but probably not eliminated) by minimizing the requirement for legal reviews. It can be mitigated by cross-training another attorney.

Business Process Reengineering (BPR)

Business Process Reengineering examines business processes with the objective of making major improvements. The general assumption is that business processes evolve bit by bit without any strategic vision to become overly complex and bureaucratic. Conventional attempts to increase efficiency result in incremental improvements – "paving the footpaths" of an obsolete process. In BPR, organizations take a completely fresh look at their processes, with the objective of slashing process time and cost by 90% or eliminating processes completely. For example, a conventional efficiency program for a customer package tracking system might streamline the telephone scripts for customer service representatives. BPR would replace the entire customer service department with a website that customers can use themselves to track their packages.

BPR thus takes the opposite approach to TQM's method of continuous process improvement. Clearly, if an obsolete business process can be reinvented at 10% the cost – with no risk of failure – BPR is the preferred approach. However, for business processes that are not obsolete, TQM is the preferred method.

Master CTAs fit the BPR model because they completely eliminate the CTA negotiation process. Or, a sponsor could create a CTA template that is acceptable as-is to most sites. The exceptions could be handled with a much smaller negotiation team or by simply refusing to modify the CTA and accepting that some sites will not do business on those terms.

Benchmarking and Best Practices (BBP)

Benchmarking and Best Practices requires multiple organizations to work together to identify the best way to do something and then adapt that approach to each organization. In a typical project, several organizations each describe in detail their way of conducting a process such as collecting accounts receivable. They compare – benchmark – their time, cost and quality metrics to identify the best process – the "best practices." The best process may exist at one participating organization, or it may require combining elements from several organizations. In this case, the most efficient organization can improve further. In many cases, one size does not fit all, so each participant adapts the results to its specific situation.

BBP projects require time and cooperation with other organizations. The big advantage is that participants to do not need to reinvent the wheel; they can just copy best practices from another organization. Another benefit of benchmarking is that participating organizations know whether their processes are, in fact, efficient. It is common for participants in benchmarking projects to discover that their internal improvement projects have been "putting lipstick on a pig."

With general business processes such as accounts receivable collection, organizations from different industries can cooperate without fear of helping a competitor or exposing a weakness. Clinical trial sponsors could, for example, benchmark their CTA negotiation process against contract negotiation processes in other industries. Cross-industry benchmarking has the advantage of exposing participants to entirely new thinking. For example, how do real estate lawyers negotiate a $30 million contract in a single meeting, while it takes months to negotiate a $30,000 CTA?

Intra-industry benchmarking has the advantage of finding differences between processes that should be very similar. These differences can translate into immediate improvements. Direct competitors will find sharing their proprietary business processes uncomfortable, but may conclude that CTA negotiation is not an area of key competitive advantage. Going into the project, it may not be clear which participant has the best practices. If the project covers several unrelated business processes, one sponsor may have the best practices in one area and another sponsor in a different area.

BBP projects can be conducted internally; different employees doing the same job have different employment histories and may have solved problems for themselves in different ways. A large organization may have its own real estate lawyers.

Competitive intelligence can provide some of the benefits of BBP. For example, sponsors can ask their sites for advice on how to improve the CTA negotiation process. Many sites, grateful for the opportunity, will describe, without naming names, how other sponsors conduct negotiations.

As a starting point, Figure 4 describes some CTA negotiation best practices.

Figure 4. Characteristics of Efficient CTA Negotiation Processes

- Enter negotiation with alternative partners so slow negotiations can be abandoned.
- Think relationships, not transactions. The first negotiation with a partner lays the groundwork for much faster negotiations in the future.
- Know who you are talking to. What are their expertise, authority, preferences and negotiating tactics? Record partner characteristics for use in future negotiations.
- Show both interest & confidence: "We are excited about your project/site and hope we can fit you in."
- Set realistic expectations. Don't ask a lion to eat grass.
- Manage negotiation as a business process. Set timelines and hold both parties to them.
- Negotiate professionally. Don't let it get emotional or personal.
- Choose your battles, assuming you want to conclude the negotiation before the study is complete.
- Prepare back-up language & FAQs so you don't have reinvent (crooked) wheels for every negotiation.
- Define roles and escalate appropriately. Empower frontline negotiators to resolve what they can, but don't let them spin their wheels on what they can't resolve. Escalate those issues without delay to the appropriate people.
- Respond quickly and meaningfully. Most time in the negotiation process is spent waiting for the other party to respond. A "no" from the legal department without any explanation may not move the negotiation forward.
- Measure performance. Measure how long each major step in each negotiation takes.
- Know when to walk away. Some negotiations are just not worth the trouble. (See point one above.)

Optimal Method for Improving the CTA Negotiation Process

There is no single optimal method for improving the CTA negotiation process. All six of the methods described above have application to the CTA negotiation process. The choice of method is a management judgment based on ambition of the goals, in-house expertise, corporate culture, project timeline, and available resources. The optimal method for a specific organization may be a combination of methods, or a piece of one method. For example, a process of incremental improvement can start generating results immediately, but the improvements may be small. A Benchmarking and Best Practices project may generate huge improvements but show no results for a year.

The six methods share common steps:

1. Identify process to improve.
2. Describe and measure current process.
3. Set goals for improvement.
4. Identify opportunities for improvement.
5. Implement improvements.
6. Measure impact of improvements.
7. Improve further until goals are achieved.
8. Control process to maintain high performance.

However, the six methods do not entirely overlap: Benchmarking and Best Practices and Risk-based Management focus on Step 4. Statistical Process Control focuses on Step 8. Total Quality Management emphasizes incremental improvements, while Business Process Reengineering emphasizes great leaps forward. Six Sigma, Total Quality Management, and Risk-based Management incorporate Statistical Process Control.

Regardless of the method, process improvement teams generally include a "business analyst" without preconceptions and one or more "domain experts" – people who know the process inside and out. Financial, statistical and other specialists may participate. Consultants often bring methodological expertise, discipline and an objective voice to the team. The longer the project, the more essential it is to have a determined executive champion to shepherd the project through the inevitable difficulties and changes in organizational priorities. The team should also consult with business partners and domain experts on adjacent processes to make sure local fixes don't create global problems.

The first step in the journey is to make the management decision that improving the CTA negotiation process is worth the trouble. After that, *all* that is required is organizational commitment and hard work.

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