Achieving More Efficient and Effective Clinical Trials

How to create and sustain improvements in critical work processes

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Pharmaceutical and biotech companies now conduct clinical trials that are more costly than ever. Although estimates of the overall average cost of developing a new drug vary – with estimates ranging from $500 million to $1.2 billion, depending on how costs are allocated – companies certainly know that whatever the cost, an increasing percentage of it is soaked up by clinical trials.

Part of the rise is due to the revolutions in biomedicine, genomics, and medical technology, as well as a focus on difficult chronic diseases, all of which have made clinical trials far more complex than in the past. At the same time, the number of patients needed to meet regulatory requirements in clinical trials has risen dramatically. This, too, has meant added time and expense.

The costs are even higher when trials are plagued by the delays and bottlenecks that result from the myriad inefficiencies commonly found in clinical trials processes, including:

- Wide variation in performance of processes
- Lack of detailed, commonly used processes
- Excessive human intervention, handoffs, and errors
- Similar activities performed in different ways
- Gaps in high-level processes and missing details at lower levels
- Wide variation in data updates and reviews

In addition, there are the "hidden" delays – time consumed that isn't regarded as delay because the company assumes that there is no more efficient way to do things. In terms of revenue alone, every day that a blockbuster drug (defined as having annual sales of $1 billion) is delayed in getting to market, the company forgoes more than $2.7 million in lost or deferred revenue.

Higher operating costs and lost revenue aren't the only prices of inefficiency. Delay can cost hundreds of millions of dollars more if a competitor gets to market first with a competing drug. Moreover, investors and analysts pay close attention to clinical trials. A reputation for efficiency can bolster a company's valuation, just as delays can depress it. In a world of rising costs, empty pipelines, imminent patent expirations, and increasing global competition, pharmaceutical and biotech companies can no longer afford the inefficient management of clinical trials.

Improving Processes: A Holistic Approach

Fortunately, companies no longer need accept inefficiencies in the execution of clinical trials as inevitable. Advances in the power and applicability of improvement methodologies and techniques now make it possible to dramatically improve the efficiency and effectiveness of clinical trial processes – from patient enrollment to data capture and compliance and more – and sustain those improvements in future clinical trials.

These techniques come from a variety of sources: Six Sigma, Lean, Lean Six Sigma, Baldrige Assessment, ISO 9000, and others. Each of those sources has its partisans, its successes, and its undeniable strengths. However, in our experience, it is far more productive to bring the appropriate tools and techniques from those disparate sources under the umbrella of a proven approach to problem-solving rather than dogmatically pursuing one narrow methodology (Snee and Hoerl, 2003, 2007). This holistic approach to improvement ensures that life sciences companies achieve comprehensive improvement in clinical trials processes, instead of pursuing piecemeal approaches that

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The Problem-Solving Framework

Experience has shown that adopting DMAIC (**D**efine, **M**easure, **A**nalyze, **I**mprove, **C**ontrol) as the preferred problem-solving and process improvement framework provides a powerful, repeatable process for continuously making and sustaining improvement. Although DMAIC is associated with Six Sigma, it can be detached from the methodology and generalized to a higher level as an overall approach to improvement. It can then be used to guide the application of improvement tools in a highly structured and sequenced approach, regardless of whether a specific tool originates in Six Sigma, Lean, Baldrige, or some other methodology. In fact, the use of DMAIC, from its initial definition of an issue forward, can help identify the most effective tools and techniques at each stage of the improvement process for a particular project.

DMAIC is easy to use and to understand. It links and logically sequences procedures and tools. It is elegant in its simplicity. And it provides a common language for improvement of any kind. Further, at a time when more and more clinical trials involve alliances with one or more partners it can also provide a common language across companies.

The Experience in Life Sciences

Many life sciences organizations have experience with the DMAIC framework through the application of Six Sigma and Lean in their manufacturing operations. Recognizing the importance of process understanding to effective process control and improvement, these companies have used these methodologies and their associated tools to increase productivity and yield, reduce deviations and lost batches, improve compliance, increase speed to market, and return millions of dollars to the bottom line.

Some companies have extended these techniques to take in what may be more broadly described as work and business processes. Some pioneering life sciences organizations are now successfully applying these approaches to their clinical trials processes (Snee and Hoerl, 2005). For example, the Clinical Operations Division of a global pharmaceutical company found that its clinical trials budget, cost, and resource management processes were performing poorly, requiring extensive effort to manage, producing large deviations from forecasts, and sub-optimizing staff skills. Moreover, the financial processes across the company's six major therapeutic areas (TAs), each with numerous trials under way at any given time, were not consolidated in a single standardized process and standardized sub-

Table 1: The DMAIC Framework

Define	Clearly identify the problem to be solved and associated financial impacts
Measure	Understand the process through various measurement tools and identify gaps
Analyze	Analyze data to determine root causes of problems
Improve	Develop and test potential solutions
Control	Sustain the gains by developing control plans to monitor key performance variables

processes. The Division's leaders decided that they wanted to standardize the process and sub-processes across TAs, reduce process variation, and provide clinical operations personnel with the skills and process improvement methods needed to improve other processes in the future.

The improvement project team divided the overall project into six sub-projects and trained leaders in the DMAIC methodology and tools. The Budget Updating sub-project illustrates the power of the approach for improving all of the clinical trials financial processes. The budgeting process, is of course, critical for the effective management of clinical trials resources. Each quarter, the Division would forecast clinical trials spend for the succeeding quarters, with particular emphasis on the year-end quarter. Based on actual spending each quarter, the forecast could then be used to re-allocate spending, as needed, to maximize the return of the funding. However, because the process was so unreliable and differed from TA to TA it was difficult to realize the benefits of reallocation.

A project team, with a finance representative and a project management representative trained to lead the effort, and four other team members, went to work:

- In the **Define** phase, a charter was developed for the team and the project was scoped to focus on improving the budget review and planning process, reducing the number of FTEs involved by 35%, and increasing the accuracy of the year-end estimate done quarterly.
- In the **Measure** phase, the team employed a variety of tools from Six Sigma and Lean. SIPOC – suppliers, inputs, process steps, outputs and customers – was used to identify each of those five elements of the Budget Updating process. Process mapping, a Lean technique, was used to understand the process and to identify non-value-added work. Cause and effect matrix analysis, a Six Sigma tool, was used to identify key variables. Through a survey, employees were asked to estimate the time they spent on the budgeting process and associated training.

  As a result of these activities, the team determined that there was no standard Budget Updating process across the TAs and that, although there were in general 17 process steps, each TA used a different process. Further, there were too many people involved with too many review steps and too many handoffs and meetings. Roles and responsibilities were unclear, and the Clinical Trial Leader (CTL) was involved too late in the process. There was high data variation and the financial system was not always used as a data source, with other "private" sources used instead.
- In the **Analyze** phase, the team analyzed one year's worth of historical data and confirmed high variation in budget forecasting: ± 25% at the TA level and ±29% at the project level. Only 8% of projects were within the project goal of ± 3%. Analysis of an additional year of data showed ± 13% at the TA level and ±18% at the project level, with only 14% of projects within the project goal of ± 3%. Analysis of the survey data highlighted lack of training for budget managers on the current quarter estimate and a lack of transparency in the budgeting system. Failure Modes and Effects Analysis (FMEA) was also conducted to identify ways in which the process could fail and the degree of seriousness for each mode of failure.

  The team concluded that the accuracy of the data at the beginning of the process needed to be improved. They also found that the

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CTL needed to have more involvement prior to budget estimate calculations to ensure correct, up-to-date data and that the budget estimates and actuals review should be part of the monthly review process. The team also noted that the existing system used a project management tool rather than project tracking tool for financial management. They also determined that estimate "placeholders" should be prohibited. Further, the system needed a central repository for budget estimates that had management approval so that teams would have a stake in the ground toward which to work.

- In the **Improve** phase, the team used the results of the Analyze phase to identify ways the process could be improved, including:
  - Standardizing and simplifying the process across all TAs
  - Reducing the process steps from 17 to 9
  - Reducing handoffs and meetings
  - Involving the CTL prior to budget estimate calculation
  - Clearly defining roles and responsibilities
  - Increasing process clarity across the organization
  - Making the financial system the single data source for budget estimates
  - Training associates in the new process
- In the **Control** phase, the team determined that management should perform monthly reviews of actual spend versus the forecast, with the Finance function annually reviewing the actual versus the forecast. In addition, for the first two years, the new process would be audited, with annual audits thereafter.

In addition to creating a common process for use across TAs and reducing process steps and handoffs, the project reduced the workload required to create the forecast by approximately 50% versus the goal of 35%. Budget managers gained a more transparent and streamlined view of budget management; the accuracy of data in the financial system was improved as was access to budget data; and management gained increased accountability throughout the process. Most importantly, the company gained the ability to reallocate available funds for maximum impact.

At the level of the entire effort, encompassing all six sub-projects, results were also substantial. Thirteen process improvements and 13 system/technology changes and improvements were made, resulting in an estimated $2.2 million in cost avoidance. Implementation plans, including training plans, stakeholder agreements and process control plans, were created for all process and system improvements and changes. In addition, the organization was left with ten project leaders skilled in the methodology and a cadre of project champions adept at supporting such projects in the future.

The example illustrates a number of key features and advantages of a DMAIC-guided, holistic approach to improvement. It begins with the premise that improvement happens project by project. Its methodology entails a carefully sequenced set of steps; it relies on rigorous empirical observation as well as data analysis, and it seeks not merely to correct individual "defects" but also to get at the root causes of variation in processes and fix them once and for all. Moreover, it is clearly applicable to any clinical trials process.

For example, a top-ten pharmaceutical company that supported a large number of clinical trials using electronic case report forms found that the process was consuming 12-15 weeks versus the company's goal of 8-10 weeks. A small team of consultants, skilled in the DMAIC

improvement approach, worked with the company's Electronic Data Capture (EDC) staff to create a continuous improvement process that draws on the tools of Lean and Six Sigma as appropriate. The first wave of improvements included ten projects worth $2.5 million in cost avoidance. Twelve members of the professional staff were trained in the methodology and successfully completed their projects in 4–8 months. Each project involved a team of 2-4 people in addition to those project leaders, thus exposing a large percentage of the EDC workforce to the methodology.

The teams made significant improvements in many sub-processes and better coordinated and aligned decision-making between line and staff functions, all with fewer FTEs. With fewer issues to be resolved between key areas, the overall time to build an electronic case report form was decreased by approximately one third, from 12-15 weeks to 8-10 weeks, enabling greater speed to market of newly released drugs. The managers and professionals in the EDC group also acquired the improvement skills needed to conduct other improvement projects in the future.

Other life sciences organizations have achieved similar gains (see Sidebars 1 and 2) Nevertheless, other industries are way ahead in using these techniques in business processes. In financial services and healthcare, for example, major bottom-line savings are being generated by improvements in processes such as billing, accounts receivables, human resources, legal, finance, and travel.

The opportunity for improvement in clinical trials processes is both enormous and obvious. The potential benefits from improving the patient enrollment process alone are worth the

Sidebar 1: Clinical Trials Efficiency Improvement

A major pharmaceutical company that supports a large number of clinical trials conducted by third parties was experiencing process inefficiencies that were causing excess cycle time in Phase IV third-party studies. Problem areas included contract negotiations, protocol development, and drug supply. Ambiguity in roles and responsibilities was also creating unnecessary hand-offs and uncertain follow through. In some areas, there weren't enough FTE resources available to effectively support and track third-party studies. Further, the IT system was not user-friendly or transparent enough to effectively track and communicate third-party study information.

To design an efficient method for conducting the Third Party Studies (TPS) process, building upon current internal procedures and Phase IV guidelines, the company adopted a team-based approach to defining opportunities for improvement and developing solutions. Working with consultants skilled in the DMAIC problem-solving approach, the team made the following improvements to the process:

- Created clinical project teams with dedicated resources for TPS
- Established a triage process to identify priority TPS, and appointed a study shepherd for them
- Began routine TPS priority project review meetings
- Established approved contract limits to expedite negotiations
- Created a steady-state drug inventory and used bulk packaging and site labeling where possible
- Appointed dedicated drug demand manager(s)
- Standardized proposal evaluation tools across brands
- Supported the initiative for an external vendor to package, label, and distribute the drug supply
- Established a regulatory SOP for TPS

As a result, the company now has a more streamlined, effective process for conducting Phase IV, third-party studies.

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effort. It has been estimated that more than 80 percent of clinical trials fail to meet their deadline for patient enrollment, a problem that contributes to 85-95% of the lost days in clinical trials (Barnes 2006). There are similar opportunities in such processes as study start-up, site recruitment, protocol development, document submission, and investigator payment. Additional opportunities include:

- Cycle time reductions for key steps
  - Toxicology studies
  - Analytical method development
  - Hiring R&D personnel
- Error reduction in key processes
  - Stability of formulations
  - R&D budget variances
  - Pharmacology test failures
- Productivity or cost efficiency
  - Purchase of consumable lab supplies
  - Reduction of number of excess documents
- Billing accuracy, methods for external contracts, invoice payments
- Reduction of process cycle time and failures

Using a DMAIC-guided, holistic approach to improvement, pharmaceutical and biotech companies can improve these and the dozens of other work processes that clinical trials entail, saving millions of dollars annually, getting to market faster, and increasing shareholder value, particularly if they also master one of the most difficult issues of improvement – sustaining the gains.

Holding the Gains: Robustness and Sustainability

No matter what improvement methodology is employed, holding the gains in improvement has often proven to be far more difficult for many organizations than they expected. Some deterioration in performance of any system left to itself is inevitable – the condition of entropy embodied in the second law of thermodynamics. Further, particular processes are also plagued by the reintroduction of error and variation as a result of their specific circumstances.

In clinical trials processes, those circumstances include a high level of employee turnover due to stress, burnout, and trials that stretch out over long periods of time. Further, much human intervention is required in the processes, including data-capture – and human beings are far and away the leading cause of mistakes. Without clear processes and guidance people do the best they can, resulting in high variation and lack of agreement on best practices. In addition, many personnel are unaccustomed to thinking in terms of processes and metrics – keys to sustaining process performance. From a management point of view, leaders may underestimate the magnitude of the culture change required to permanently change the way the organization works

However, by far the major cause of deteriorating performance is the tendency of organizations to focus on sustaining gains only after the improvement has been achieved. Intuitively, that may seem the correct sequence, but it is in fact backwards. Although maintaining the gains comes chronologically only after an improvement project has been completed, sustainability should be an integral part of the design or redesign of any clinical trials process from the first (Snee 2006). It involves two chief elements:

- Designing or redesigning processes to be robust
- Planning for sustainability at the strategic and tactical levels

Failure to do either of these things virtually guarantees that improvements won't last.

Creating Robust Processes

It is not enough for processes to be efficient and effective; they should also be robust if their performance is not to deteriorate (Snee, 1993). A robust process is insensitive to uncontrolled factors both internal and external to it. It is like installing shock absorbers on a car. Shock absorbers enable passengers to enjoy a smooth ride despite the uncontrollable conditions of the road. Similarly, robustness provides shock absorbers for the work process and its output.

A robust process is more likely to perform as expected because problems have been anticipated in the design of the process and preventive measures have been built into it. For example, employee turnover, which is often high in clinical trials work, can potentially hamper many processes. Personnel who leave may take their knowledge of how to execute key processes with them. New personnel require training and they are likely to make mistakes during their learning period. However, if the processes are designed on the assumption that such turnover is likely, the adverse consequences of turnover can be avoided.

Designing a robust process begins with the development of a deep understanding of that process. It is impossible to improve or control a process that is not well understood. Process understanding leads to accurate prediction of process performance, and if process performance can be predicted, it can be controlled.

Sidebar 2: Improving Clinical Trials Data Management

The worldwide clinical data management organization for a major global pharmaceutical manufacturer was experiencing problems with its clinical data entry system. This critical system, in which all of the key variables and parameters are entered from patient case report forms, lacked statistically sound sample sizes and accept/reject limits required for accurately assessing error rate performance. As a result, government regulators challenged its validity. Further, lengthy cycle times for when the patient visited the physician at the field site to when the visit was entered and reviewed in the clinical trial database (i.e. "visit-to-data-review-complete") were slowing the entire trials process, and making the process of correcting errors more time consuming and therefore more costly the farther back in time the source of the error receded.

A joint consultant-company team, using DMAIC methodology, designed a valid sampling plan that allows the company to sample data post-certification to ensure acceptable error rate performance. The team also identified the key drivers for the "visit-to-data-review-complete" process for five data management centers on three continents and made improvements that brought the process under statistical control. The team also instituted a general statistical process control (SPC) plan for the world-wide clinical data management organization at the strategic, tactical, and operational levels:

- Executive SPC Reporting to enable "big picture" monitoring at the level of the therapeutic area (TA)
- Process SPC Reporting to enable monitoring at the level of the data system
- Site SPC Monitoring to enable near "real-time" SPC

The team also introduced the organization to new statistical tools and trained select individuals in the use of statistical software.

As a result of these improvements, the clinical data management organization gained a far more statistically defensible data entry system, a better understanding of the drivers of superior data entry performance, and improved monitoring at every level of the organization to ensure the accurate and efficient data entry required to keep clinical trials on the fast track.

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Again, the key is to employ a holistic approach to improvement that draws on the appropriate tools for the process and the problem. For example, depending on the particular clinical trials process and problem that has been identified in the Define phase of DMAIC, robustness might be achieved through Failure Modes and Effects Analysis (FMEA) from Six Sigma to identify and prioritize the uncontrollable factors during the Measure and Analyze phases. Lean tools like mistake-proofing (in the likely event of human error) and videotaping (if inadequate training is likely to cause problems) might then be used in the Improve and Control phases to ensure robustness of the process.

The idea of mistake-proof, user-friendly, flexible processes is not new. Nevertheless, most companies do not routinely consider robustness when they are designing their work processes.

Planning for Sustainability

At the strategic level, achieving sustainability depends upon putting in place the requisite management processes to guide and sustain the initiative. Slipshod planning and inadequate deployment of improvement initiatives almost guarantee the inability to sustain whatever gains might initially be achieved. This is strategic because it entails embarking on the effort with a clear roadmap to success and the resources to win. At this level, there are three key factors that determine success:

- *Management leadership and involvement.* Senior leaders must lead improvement efforts with relentless enthusiasm and energy. Simply "supporting" the effort through speeches, emails, and the like doesn't suffice. Leaders must give time, attention, and resources to the effort.
- *Use of top talent* – Improvement is too important and difficult to be left to anyone other than the best people possible. Using top talent sends the clear message that leadership takes the effort seriously.
- *Creation of infrastructure* – To establish an improvement initiative in the larger strategic context it is more productive to regard it not merely as a technique but as an infrastructure. This infrastructure comprises four components: the structured DMAIC approach to problem-solving, proven improvement tools, a cadre of improvement leaders, and appropriate management systems.

At the tactical level, the first six months of an improvement initiative are critical for securing some early wins, demonstrating the initiative's effectiveness, and establishing a rhythm of identifying, launching, reviewing, and completing individual projects in the overall effort to improve clinical trials processes – and then moving to the next round of improvement projects. Individual improvement projects should have these characteristics (Snee 2001):

- Manageable scope
- Clear connection to business priorities, linked to strategic drug development plans
- Ability to produce significant improvements in process or performance of >50% or to generate major financial improvements
- Clear importance, inducing people to support the projects
- Clear quantitative measures of success
- Management support and approval

At the end of the first six months, when it's time to start the next wave of projects, the organization should be in a position to sustain the gains already made and have acquired the capability to repeatedly apply the DMAIC improvement approach and hold the gains it brings.

The Risk of Delay

The approach is proven; the tools powerful; and the business case persuasive. The holistic, DMAIC-guided problem-solving methodology has improved business and work processes across industries, including life sciences, where it is now being applied in every stage of drug development and commercialization. Its tools, drawn from Six Sigma, Lean, and other improvement approaches, provide rigorous data-driven techniques that reduce process variation, identify and eliminate root causes of problems, and ensure that improvements endure. The return on investment is potentially enormous. In our experience, small to medium-size companies that institute this approach enterprise-wide realize savings equal to 3-4% of revenue per year. The savings for large organizations is in the range of 1-2% of revenues per year. In both cases, these savings accumulate year over year if the company is able to sustain the improvements.

But there is an even more compelling reason for undertaking the effort: competitive viability. Recent business history is littered with examples of companies long thought to be invincible – think of some venerable names in the automotive and steel industries –finding themselves eclipsed by companies that were first to adopt improvement approaches like Six Sigma and Lean. With costs rising and global competition increasing, leading life sciences companies are working diligently to streamline their drug development processes not only to save money but to accelerate their velocity to market. The companies that master process improvement are most likely to win the race.

These companies will win in another way as well. As improving existing processes and creating new ones becomes increasingly important for remaining competitive, the ability to lead such change will become more critical for company leaders. Improving clinical trials processes, and similar improvement efforts, not only generates gains in efficiency and effectiveness but also provides a crucible in which the next generation of leaders and change-agents is forged, providing the company with an extra edge in talent and leadership. It's an unbeatable combination: performance improvement and improved performers.

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