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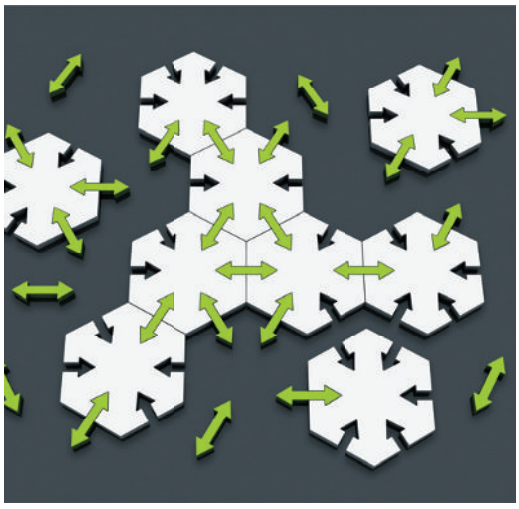

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Quality Drivers in Clinical Trial Conduct

Michael J Howley PA-C, PhD, and Peter Malamis, MBA

Identifying the performance metrics that have the greatest impact on clinical trial quality.

The clinical trials industry has demonstrated a commitment to improving the quality of clinical trials. Over the past decade, a variety of quality initiatives have emerged and billions of dollars have been invested to improve the quality and performance of clinical trials. New quality management techniques like risk-based monitoring and Quality by Design (QbD) have also become popular. Despite these efforts and investments, however, there has been little impact on the quality of clinical trials.

We believe that these quality efforts and investments have had limited impact because we have been using the wrong quality measures. It is common practice, for example, to use manufacturing quality indicators like the number of days to recruit or the number of queries during the trial. But these don't measure quality—one is a measure of time and the other is a defect rate. These indicators are performance drivers that may be related to quality. Quality is a different construct that must be measured separately. And since a clinical trial is a type of professional service, it is important to measure the service quality of the clinical trial.[1,2,3] Once the service quality has been established, the other performance metrics can then be related to clinical trial service quality.

While measurement may seem like a mundane detail, it is a critically important issue. First of all, regulators "…require sponsors to monitor the conduct and progress of their trials..."[4] that should continue "… on a continuous basis throughout the design, conduct, evaluation, and reporting of the trial."[5] If you are not using the right measures in your oversight, then you can't properly and efficiently monitor your trial. Perhaps more importantly, failure to detect impending quality failures delay trials and are costly. Unless the industry adopts valid and reliable measures of quality and critical performance drivers, then they will not be able to improve the quality of clinical trials.

The purpose of this research is to assess the quality within the conduct of clinical trials and then identify the key drivers of performance within study conduct and relate them to quality. In doing so, we identify the performance metrics that have the greatest impact on clinical trial quality.

Methods

We focus on quality within the conduct of the trial (as opposed to study startup or closeout). To measure the service quality of the conduct of the trial, we used a single-item global indicator.[6] Since it is common practice within the industry to use operational metrics as proxy indicators for quality, we had to adopt an exploratory posture to identify the performance metrics we should assess. First, we sought to create a comprehensive list of performance drivers. We interviewed a series of clinical trials managers over the course of 18 months and asked them to list all of the performance activities that impact the quality of trial conduct. Both sponsors and CROs were included in our sampling. We continued to interview managers until we were no longer identifying new quality drivers. In all, 36 interviews were conducted. Respondents identified

seven general areas that were important to conduct quality, including: adaptability, adherence, enrollment, functions, monitoring, project manager, and site relations.

Second, we then performed a quantitative analysis to distill all of these measures down to the essential indicators and calculate the magnitude of the relationship of each indicator to conduct quality. To do this, the items were loaded into an online survey tool. All of the items were edited for clarity and grouping. Sponsor and CRO trial managers were solicited in a purposive sampling to complete the survey, excluding respondents from the qualitative phase. *Applied Clinical Trials* collaborated in the data collection.

We received 82 usable surveys with 37% from Phase II trials, 46% from Phase III, and 17% from Phase IV. The average number of sites was 74 with an average 558 subjects.

We used the statistical program SmartPLS 3 to identify the essential indicators of conduct quality. Missing data was less than 5% of all variables except for data management, protocol amendments, and project management with less than 10% missing data. For these cases, the missing data points were imputed. All of the items had acceptable univariate and multivariate normality. All variables used a 1 to 10 scale, with the exception of the covariates (phase, sites, subjects, and a dummy sampling variable).

Within the seven important areas identified by managers in the first qualitative phase of our research, adaptability was a formative construct consisting of protocol amendments, change order processes, managing protocol violations, and resolving queries. Only protocol amendments (β= .31, t = 2.67, p= .009) and change order processes (β= .31, t = 2.54, p= .01) were significant and only these two items were included in the adaptability index. Adherence was a reflective construct assessed by adherence to both the study protocol (γ= .88, t = 21.2, p< .001) and the medical management/safety plan (γ= .87, t = 15.3, p< .001). Enrollment was constructed as a formative indicator and was assessed by evaluating the performance of the clinical study team on enrolling patients that met the criteria and keeping you up-to-date on the enrollment process as well as timeliness in first site, last site, first patient, and last patient. Only adhering to the timeline for enrolling the last patient (β= .87, t = 4.43, p< .001) was significantly related to enrollment performance and so was used as the enrollment indicator. Performance on the functions was structured as a reflective indicator and included project management (γ= .81, t = 18.9, p< .001), data management (γ= .90 t = 34.3, p< .001), regulatory (γ= .90, t = 40.8, p< .001), centralized diagnostic service (γ= .86, t = 25.1, p< .001), CRF tracking (γ= .83, t = 21.7, p< .001), and external data sources (γ= .87, t = 25.8, p< .001) and were all scaled into the latent functions construct. Performance of the project manager, site relations and routine monitoring visits were all measured as a single global indicator.[8] All of the latent constructs had reliabilities > .89, discriminated from each other, and established acceptable validity.

Once the measurement model was established, we examined the magnitude of the relationships between the performance drivers and conduct quality in a regression equation model using SAS 9.3. All variables were mean-centered prior to estimation, so the coefficient describes the relationship of the predictor on conduct quality at the average of all the other factors.

Results

The model performed well (F10,71 = 29.2, p< .001) and explained a substantial amount of the variance (R2 = .80) of conduct quality. The means, standard deviations, and correlations of the variables used in the statistical analysis are shown in Table 1.

Table 1: Descriptive Statistics Results

	Mean	Std Dev	Adap	Adher	Con Qual	Enroll	Func	Mon	Proj Mgr	Site Rel
Adaptations	6.5	2.25	1							
Adherence	6.2	2.23	.74	1						
Conduct Quality	7.2	1.61	.80	.63	1					
Enrollment	6.4	2.52	.79	.69	1					
Functions	6.9	1.88	.78	.67	.73	.73	1			
Site Relations	6.5	2.05	.53	.40	.42	.58	.51	1		
Project Manager	6.8	2.19	.78	.64	.82	.76	.71	.46	1	
Site Relations	6.4	2.27	.80	.70	.79	.75	.73	.54	.72	1

Source: Howley, Malamis, 2015.

Table 1. All variables were mean-centered prior to estimation, so the coefficient describes the relationship of the predictor on conduct quality at the average of all the other factors.

The relationship between the performance activities and conduct quality are illustrated in Figure 1. The magnitude of the coefficient describes the strength of the relationship between the driver and conduct quality. The coefficient for adaptability (β= .20, t = 2.12, p= .04) is interpreted, for example, that a 1 unit increase (on a 1 to 10 scale) in the adaptability of the study team improves conduct quality by .20 at the average levels of adherence, enrollment, functions, monitoring, project manager, and site relations. Given the scaling, you could also describe this as 'a 10% increase in study team adaptability improves quality by 2%.'

There was a negative but non-significant relationship between adherence (β= -.11, t = -1.02, p= .31) and conduct quality. While the coefficient estimate is negative, the non-significant coefficient means that we could not identify a relationship between adherence (to the medical management, safety plan, and study protocol) and conduct quality.

Enrollment (β= .18, t = 2.32, p= .02) as positively and significantly related to conduct quality. Improving enrollment by 10% increased conduct quality by 2% at the average levels of all the other conduct quality drivers. The various functions (β= .13, t = 1.22, p= .22) involved in a trial did not improve quality. The project manager (β= .35, t = 3.69, p< .001) had the greatest impact on project quality. Improving project manager performance by 10% increased conduct quality by 3½%.

Managing site relationships (β= .31, t = 3.17, p= .002) had the second greatest impact on conduct quality. The routine monitoring visits (β= -.15, t = -1.86, p= .06), however, had a negative and marginally significant impact on project quality. There was not a significant (β= .02, t = 0.65, p= .51) interaction between site relationships and the routine monitoring visits. Regardless of the status of site relationships, the routine monitoring visits degraded conduct quality.

The covariates in the model, including phase (β= -.23, t = -1.25, p= .26), sites (β= .06, t = .93, p= .18), and subjects (β= .00, t = .04, p= .48) were all insignificant.

In summary, the most impactful drivers of conduct quality were the project manager and site relations. Enrollment and the adaptability of the study team had lesser but positive effects on conduct quality. Routine monitoring visits had a negative impact on quality.

Discussion

The ability of a manager to oversee a clinical trial depends on having scientific measurement instruments to provide a clear view of what is going on in the trial. We believe that all of the efforts and investments in clinical trial quality over the past decade have had a limited impact on trial quality because of the industry's exclusive focus on operational metrics. We have been using, in other words, the wrong performance metrics. It is remarkable that it is not common practice in the industry to directly measure the quality of clinical trials. The purpose of this paper is to illustrate how sponsors should measure the quality of clinical trials and identify the various performance drivers that drive quality.

A major contribution of this paper is to quantify the magnitude of the relationship between each of the performance drivers and conduct quality. This result allow managers to identify the most important and substantial drivers of quality. In this way, the approach to quality measurement is efficient because you can focus on the few drivers (i.e. project manager, managing site relations, project manager performance, and enrollment) that will impact conduct quality. At the same time, this approach is comprehensive. We know we have captured the major quality drivers because the R2 was 80%. While these analytical methods carry off-putting names like regression modeling, predictive analytics, or business analytics, these techniques can be performed on an Excel spreadsheet. These are basic analytical techniques that should be more often within the clinical trials industry.

Another contribution of this study is to directly measure the quality of the trial. This is unusual in the clinical trial industry. In our five years of research in this area, we have not yet been able to identify any previous assessments that captured the overall quality of a clinical trial. A critical step in clinical trial quality measurement is to recognize that a clinical trial is a service and not a manufacturing process. Quality measurement techniques, as a result, have a different look and feel than the operational metrics used in manufacturing. We occasionally find managers are uncomfortable with this services approach because they apply the manufacturing analogy to clinical trials. But using manufacturing instruments to measure service performance and quality is misguided and provides invalid and biased results.

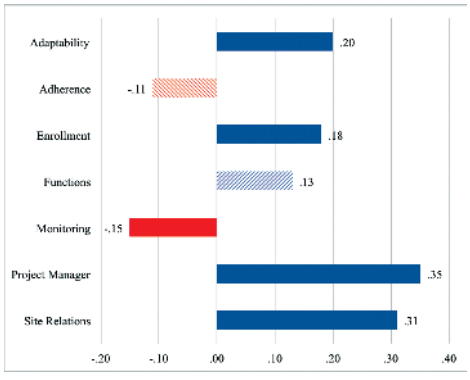
One benefit to focusing on service quality is that it cuts across all of the organization's silos. Our measures, for example, included protocol amendments, medical management and safety plan, regulatory, external data sources—all coming from various parts of the CRO or sponsor organizations. Since service quality is generated from across the organization, it is important to draw assessments from across all parts of the company. We have found that C-level executives, in particular, appreciate this feature of quality measurement.

What should we make of the insignificant drivers of quality in this analysis? In interpreting these results, it is important to remember that this research consisted of two stages—the initial qualitative phase where experienced executives identified all of the key drivers of clinical trial quality. The purpose of the quantitative analysis in the second phase of the trial was to examine how changes in the drivers impacted quality. An insignificant coefficient simply means that changing the level of the driver does not change quality. An insignificant coefficient does not mean that it is not an important contributor to a quality trial. A driver's importance was established when it was included in the executive interviews.

We understand insignificant drivers of quality to be a type

of hygiene factor as compared to enhancing (a.k.a. motivating) factors.[7,8] That is, there are hygiene drivers of quality that do not work to increase quality, but will degrade quality if they are not present. Enhancing factors increase quality as they are improved. The results of this study should not suggest that it is not necessary to adhere to the medical management, safety plan, or study protocol. Improving these factors, however, will not improve conduct quality.

Figure 1: Drivers of Conduct Quality



Source: Howley, Malamis, 2015.

Figure 1. The most impactful drivers of clinical quality were the project manager and site relations.

Finally, the results of this study have three important implications for risk-based monitoring. First, the negative relationship of monitoring visits to conduct quality and the positive effects of site relations suggests a complex relationship between attempts to maintain data integrity and conduct quality. We believe that risk-based monitoring efforts must be guided by scientific and valid performance metrics using leading indicators of performance (e.g. adherence and enrollment performance). Attempts to use operational metrics to guide will lead to a backward view of the clinical trial (i.e. they are lagging indicators) and to gaming by the sites.

In summary, we believe that adopting scientific quality measurement that recognizes that clinical trials are a service will allow the clinical trial to reap the benefits of all their efforts and investments. At the same time, the approach described here meets regulatory requirements for oversight of clinical trials. The primary advantages of this approach are first, comprehensiveness. Our model captured 80% of the variance in conduct quality, meaning that we have identified the major drivers of quality. Second, this approach is efficient. Subjects took an average of 4 minutes and 38 seconds to complete the assessments. Third, these measures are meaningful. We established the validity of the assessments in the measurement model analysis. In comparison, operational metrics lack validity. Fourth, these measures are objective. Ideally, these assessments would be administered by an independent third party, but many of the interpersonal biases typical in assessments like this are eliminated because we are assessing organizational quality and performance. Finally, these assessments are reliable as established in the measurement model.

Note: Variables illustrated with solid colors are considered statistically significant (p>.05). Variables illustrated with cross-hatched colors are not statistically significant.

Michael J Howley PA-C, PhD, is the Associate Clinical Professor of LeBow College of Business at Drexel University, Peter Malamis MBA, is the CEO, CRO Analytics, LLC.

References

1. M. Howley and P. Malamis "The Quality of Clinical Trials." Applied Clinical Trials, available at http://www.appliedclinicaltrialsonline.com/quality-clinical-trials (accessed on February 20, 2015).
2. M. Howley, "How We Fall Into Metrics Malpractice," Applied Clinical Trials, May 27, 2014, available at http://www.appliedclinicaltrialsonline.com/node/245666, (accessed on February 17, 2015).
3. M. Howley, "The Next Generation of Clinical Trial Performance Measurement," Applied Clinical Trials, Feb 27, 2014, available at http://www.appliedclinicaltrialsonline.com/next-generation-clinical-trial-performance-measurement. (accessed on February 26, 2014).
4. United States Department of Health and Human Services Food and Drug Administration "Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring," August 2013 (pg.2).
5. "Reflection Paper on Risk Management in Clinical Trials," European Medicines Agency, November 18, 2013 (pg. 7).
6. L. Bergkvist and J.R. Rossiter. "The Predictive Validity of Multiple-Item Versus Single-Item Measures of the Same Constructs." Journal of Marketing Research 44(2) 175-184 (2007).
7. R. Johnston, "The Determinants of Service Quality: Satisfiers and Dissatisfiers." International Journal of Service Industry Management 6(5) 53-71 (1995).
8. F. Herzberg, B. Mausner and B. Snyderman, The Motivation to Work, (Wiley, New York, 1959).
9. M. Howley and P. Malamis, Clinical Trial Performance Measures You Can Use (and believe), Clinical Leader, October 2013 http://www.outsourcedpharma.com/doc/clinical-trial-performance-measures-you-can-use-and-believe-0001

Speeding Negotiations with Investigative Sites

Lucas Miller Glass

Tailored grant proposals bring benefits to sites and sponsors with decreased time spent on contracts.

Every good negotiator understands that "success in negotiation is directly related to the amount and kind of preparation preceding the negotiations.[1] Many leaders in clinical operations may not realize, though, just how much information is available to help them as they prepare grant proposals for investigator sites. Sponsors can, in fact, enter into negotiations with sites armed with great insight into what each site is likely to accept as payment for study participation. And, the closer sponsors are to hitting that mark with their initial offer, the shorter the negotiation cycle. IMS Health analyzed data on 16,240 grant offers and contracted budgets to understand the impact that tailoring the initial contract value has on the success and speed of the whole process.

The R&D pharmaceutical industry spends an estimated $12.3 billion each year in clinical trial grants to investigator sites, accounting for about 10% of all R&D spending. The negotiation process—the back and forth and give and take—with clinical trial sites before contracts are signed is one of the most unpredictable aspects of study start-up. Most sponsors aim to complete site negotiations with a given site in less than 20 days, but their ability to do so is quite varied. More than 23% of contract negotiations extend beyond 60 days. Also, the median length of the negotiation cycle is tied to the study phase, as shown in Figure 1. Typically, it takes 46 days to negotiate a Phase I study and 28 days for a Phase III study. Clearly, the more defined the protocol is, the less perceived risk there is in settling on prices and the less negotiation time is required to come to an agreement.[2]

As research progresses, the protocol becomes increasingly established and there are fewer unknowns in the budgeting process, so negotiations are resolved more quickly.

Figure 1. Median Negotiation Cycle Time by Phase

Phase	Days
I	46
II	29
III	28
IV	19

Source: IMS Health

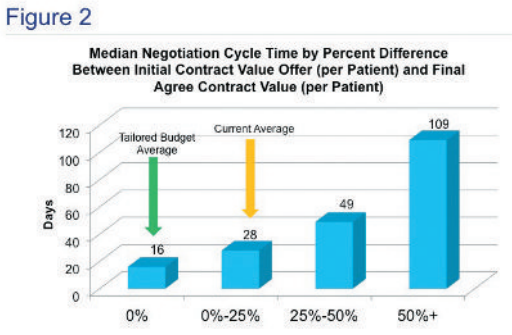
Figure 1. As research progresses, the protocol becomes increasingly established and there are fewer unknowns in the budgeting process, so negotiations are resolved more quickly.

About the study: An analysis of grant offers vs. contracted budgets

What other variables, aside from study phase, affect negotiation cycle time? Could the degree to which offers are tailored to the contract history of specific sites have an impact on negotiation timelines? How close can sponsors come to offering what sites will accept, and how much can that speed negotiations?

To answer these questions, we analyzed data

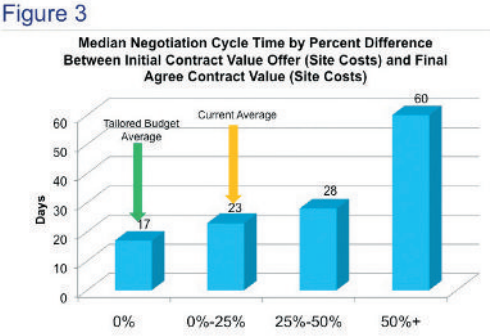
Figure 2. Per-Patient Costs



Source: IMS Health

When the final contract value for per-patient cost is 50% or more higher than the initial offer, the contract takes an average of 109 days to negotiate—nearly four times longer than offers that were within 25% of the final contract value.

Figure 3. Investigative Site Costs



Source: IMS Health

When the final contract value for site costs is at least 50% higher than the initial offer, the contract takes an average of 60 days to negotiate—nearly three times longer than for offers that were within 25% of the final contract value.

on clinical trial agreements (CTAs) stored in an online negotiation tool through which sponsors and investigators submit offers and counteroffers on clinical grant costs. The data, extracted from our GrantPlan® database, included contract details on 16,240 clinical trials negotiated between September 1, 2010 and September 1, 2015. We compared the initial, time-stamped offer to the site with the final, time-stamped agreed-upon budget, and measured the time in between. Comparisons were made for per-patient treatment costs and one-time site costs such as electronic data capture (EDC) system training expenses, institutional review board (IRB) applications, and patient outreach to support recruitment.

Finding 1: Cycle time is tied directly to size of the value gap

How much price negotiation actually takes place between sponsors and sites before trial contracts are signed? On average, the final costs that are agreed upon between sponsors and sites are 8% higher than the original offer for per-patient costs and 17% for site costs. The difference by type of costs very likely reflects the fact that patient treatment costs are well established in the medical community, whereas there is naturally greater variability in the start-up and administrative costs that various sites incur in preparation for study participation.

The further away the initial offer is from what is finally agreed upon, the longer negotiations will take, both for per-patient costs and one-time site costs. While this conclusion might have been anticipated, it is worthwhile having empirical data to confirm that this as the case (see Figures 2 and 3). In fact, companies lose 1.4 days to negotiation for every percent that their initial offer is away from the final, agreed-upon amount.

When the final contract value for per-patient costs is 50% or more higher than that of the initial offer, the contract takes an average of 109 days to negotiate. That's nearly four times longer than for offers that were within 25% of the final contract value.

When the final contract value for site costs is at least 50% higher than that of the initial offer, the contract takes an average of 60 days to negotiate. That's close to three times longer than for offers that were within 25% of the final contract value.

Finding 2: Tailoring the initial offer can reduce negotiation time by a full week

Currently, more than half of the time (54%), sponsors approach all the sites in a given country with the same initial offer. In other words, they do not tailor their proposed rates by the type of site, much less the specific contracting history of each one.

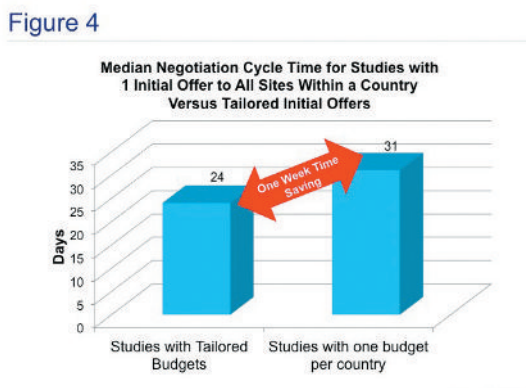
Figure 4 illustrates how the negotiation timeline can be shortened by a full week when the initial budget offer is tailored to the individual site. These results are for per-patient and site costs, combined.

The median time required to negotiate contracts with sites can be shortened a full week—from 31 days to 24 days—by tailoring the initial offer based on historical data on that site.

Finding 3: Negotiation cycle time is more sensitive to changes in per-patient costs than site costs

When the initial offer for reimbursed per-patient costs is tailored to the site's history (and presumed expectation), the contracting process is shortened by 12 days over the current average of 28 days. The comparable reduction is six days with site costs.

Figure 4: Initial Tailored Offers



Source: IMS Health

Figure 4. The median time required to negotiate contracts with sites can be shortened a full week using tailored proposals.

Finding 4: Contracts are more likely to be signed when the initial offer is customized to the site

Negotiations conducted around tailored budgets failed to conclude in a contract 5% of the time, compared to 9% of the time for "boilerplate" offers extended to all sites within a country. That represents a 44% loss in opportunity. These findings, however, must be regarded with a caveat: companies are more likely to tailor their offers to sites with whom they've worked in the past because they have some historical experience on which they can draw. This also means that they have established a relationship with those sites, and the existence of that relationship might account for some of the success in closing the deals with this group.

How to tailor initial offers to sites

This research confirms that there is demonstrable value in opening negotiations with sites with payment proposals that are close to what the site expects and will ultimately agree to. The question then becomes, "How can a sponsor zero in on budget proposals that are appropriate for individual sites?"

The first step is to maintain a repository of data on all contracts, by facility. These searchable details should include:

- The starting offer and date for patient treatment and site costs
- A history of the subsequent counteroffers and offers, with corresponding dates
- The names and positions of the individuals involved

When maintained at this level, a company's own records will be quite helpful in dealing with familiar sites. However, this information should, ideally, be supplemented with benchmark data from a commercially available database that incorporates the results of others' negotiations with sites across thousands of trials.

With such detailed information, it is possible to understand where different types of sites fall on the pay scale. On a broad level, for example, sponsors can understand the differences in how academic institutions vs. site management organizations negotiate. They can even get answers to more refined questions such as "What are the fees typically requested by sites that have five full-time equivalent staff members dedicated to research?"

The ultimate application of this information is to be able to know—prior to sending an offer—that a particular site, such as a university hospital, for example, typically settles for payment at the 80th percentile of the range. Knowing this is critical because the time difference between making an initial offer to this hospital in the 50th percentile vs. the 75th percentile could be weeks.

Conclusion

Sponsors can increase the predictability and speed of the contracting process with investigator sites by understanding each site's past contracting history. When sponsors enter into negotiations armed with benchmark and historical information, they can make a more realistic initial offer that is closer to what the site will ultimately agree upon. In this way, sponsors can shave valuable time—one week on average—off of the contracting stage.

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References

1. Gottlieb, M., and Healy, W. "Making Deals: The Business of Negotiating" (2nd ed.). Greenwich, CT: The Communication Project. (1998).
2. Glass, Lucas M. "Spotlight on Site Budget Negotiation Cycle Times." Journal of Clinical Research Best Practices. Vol. 11, No. 11 (2015): p.1. First Clinical Research. Web. 15 Oct. 2015.

A Guide to Risk-Based Study Start-Up

Barry Milton

Using big data to overcome cumbersome study start-up processes.

The process of initiating clinical trials is cumbersome, challenging and fraught with delays—it has the greatest impact on patient recruitment, trial duration and its associated costs, unfortunately, it is also the worst performing stage of any clinical trial. Study startup is the most resource- and labor-intensive period in a study's life cycle after data cleaning and database lock activities. According to the CenterWatch Survey of Investigative Sites in the U.S., nearly 70% of all trials experience enrollment delays[1], while nearly half complete later than originally planned[2] and one-fifth of sites never recruit a single subject[3].

Protocol complexity and increased partnering in study startup is here to stay. According to a recently released report from Research and Markets,[4] by 2020 close to three-fourths of all clinical trials will be performed by CROs. As outsourcing continues to increase (as well as the amount of data to be shared), sponsors and CROs must work on ways to collaborate by building on the strengths of each organization and utilizing information and resources in a more uniform, consistent manner. Close collaboration with CROs and taking a risk-based approach, which relies on Big Data analytics, is key to enabling rapid study startup in an increasingly complex clinical development environment.

Problem and status quo

Typically, the site nomination and selection process is collaborative and completed utilizing internal and external data supplied from either the CRO data source and/or the sponsor sources. This data is critical to the success of site selection and includes such information as:

- Site capabilities and skills
- Past performance of sites
- Background on the Principal Investigator and the institution

Too often the process is inefficient due to the lack of data availability related to operational cycle times, site submission timelines, and other factors. Without this data, the sponsor and CRO are at risk of selecting non-active or non-enrolling (NANE) sites, which ultimately drives up the costs and wastes valuable time in study startup. Currently, 80% of trials fail to meet enrollment timelines[5] and up to 50% of research trial sites enroll one or no patients.[6]

Today, most operational cycle time tracking is still conducted via Excel sheets and information cobbled from CTMS and EDC databases, which are then manipulated to provide rudimentary views of site performance. Often this cycle-time tracking is incorrect or lacks data governance and sufficient detail to be of value for decision-making. In the future, successful sponsor-CRO partnerships will require the combination of both their institutional memories with regard to site capabilities, patient availability and performance to reduce the number of NANE sites. Further complicating the decision making process for sponsors is the use of multiple CROs, with disparate systems for collecting operational data, and the inability to collect and then combine operational data into their own system.

Big data enables risk-based SSU

Tracking this low level activity completion times and cycle time data involves thousands of data points. Like other industries, clinical operations teams are realizing the challenges and opportunities that lie in effectively managing big data.

New generation systems enable teams to capture, analyze, share and visualize study startup data in one system. Trial project managers can now know if a study is on track and if not, make the required decisions to remove bottlenecks and eliminate or refine unnecessary activities to ensure that all information required for regulatory submissions are ready by the submission dates. Having access to data trends in a central location allows study teams to focus on potential risks and the most critical data and processes necessary to achieve study objectives–a risk-based, data-driven approach to study startup. There is growing consensus that risk-based approaches to monitoring are more likely than routine visits to all clinical sites and 100% source data verification to ensure subject protection and overall study quality. Like global monitoring, taking a risk-based approach to study startup is a best practice for accelerating activities from site selection through to activation. Rather than relying on individual knowledge or select outdated data, taking a risk-based approach requires that you gain insight into the key bottlenecks and processes that are most likely to affect study startup performance.

How to implement risk-based SSU

Establish Data Transparency. The first pivotal step involves increasing transparency in study startup to enable identification of key trends and processes. Having data in multiple locations with multiple partners is an obvious bottleneck. Efficient site selection requires that organizations combine both internal and external data sources. Data sources may include both in-house repositories such as CTMS, investigator databases, feasibility surveys, quality/risk Assessment information, as well as third party sources such as epidemiology data, site performance data, and subject availability. This data warehousing enables study teams to compute selection and performance variables, which ultimately drives improved decision-making regarding site selection.

Promote Collaboration Across the Study Team. It is not enough to have central access to a comprehensive data repository. Globally dispersed study teams need a way to collaborate in real-time and track milestones, role assignments, site selection, and study startup progress. During site selection and into site activation, protocols may change and key processes may be impacted by external factors or general unforeseen challenges. The team needs to be able to watch these changes/trends and change course accordingly to move the study forward. That means being able understand risks in advance to be able to pivot team members onto critical task where risks are identified. Which can only be accomplished with transparency of the trends and the allocation of team members across multiple trials and activities.

Identify and Optimize Key Processes. With the data warehouse in hand, it is essential to track study activation and real-time cycle time metrics as the study proceeds. This provides visibility into the success of your site recruitment strategy, allowing you to identify risks and put mitigation plans into place ahead of time.

Monitor Progress though Routine Data Visualizations. Data visualization is an on-going activity, which should have dedicated resources to enable proactive risk management. Data visualization with predictive trend monitoring allows teams to see risks better than numbers in a columnar view like Excel. Performing data visualizations with historical and just in time data can help teams mitigate risk factors to recruitment and retention by finding the optimum alignment of top performing sites with high patient availability. Teams can then quickly assess which sites have performed best in past studies on a variety of performance categories, such as startup, throughput, retention and quality.

Don't Forget End-to-End Lifecycle Optimization. End-to-end lifecycle optimization should be considered as part of any solution for optimizing study startup. To activate sites on-time and meet enrollment targets, you must take a holistic view of the process, looking at potential bottlenecks and how they may impact downstream activities. Being an informed team allows for proactive mitigation of bottlenecks for sites, which have great potential but are in need of support to be fully efficient in the executing of the study.

Complexity in study startup is an everyday reality that is here to stay, but a risk-based study startup approach, which relies on a centralized, data-driven approach integrating insights and processes within the sponsor team and in collaboration with CRO partners, can position clinical trials for ultimate success.

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References

1. CenterWatch Survey of Investigative Sites in the U.S. (2009).
2. Gwinn, B. Metrics for Faster Clinical Trials. PharmaVOICE.
3. Enrollment Performance: Weighing the "Facts." (2012, May). Applied Clinical Trials.
4. Research and Markets Report "Research and Markets: The New 2015 Trends of Global Clinical Development Outsourcing Market" http://bit.ly/1RB2GhE
5. Kremidas, Jim. Recruitment Roles: Sponsors, CROs, and investigator sites must all work together for effective patient recruitment. http://bit.ly/1QnPIES
6. Miseta E., Bring Down the Cost of Clinical Trials With Improved Site Selection. Clinical Leader: http://www.clinicalleader.com/doc/bring-down-the-cost-of-clinical-trials-with-improved-site-selection-0001?atc~c=771+s=773+r=001+l=a

An Ideal SOP System

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While the number of SOPs are increasing, there is no evidence that quality or efficiency is improved.

This article aims to define guiding principles and to establish a framework to set up an ideal standard operating procedure (SOP) system. Only a few articles dealing with what constitutes ideal SOPs have been published.[1] Rather than examining a few SOPs in a certain area or just the documents that carry such titles, it may be advantageous to take the entirety of all documents that describe relevant processes and call this an "SOP system." SOPs are not usually standalone documents, but they are linked to each other and to other systems, such as policies, handbooks, guidance papers, or instruction documents. The definition of those items unfortunately varies and are used by different companies or institutions in different ways. In some cases, policies are above SOPs in hierarchy, which, in turn, are above guidance documents and, lastly, instruction papers. Common to all is a hierarchical structure of governing and dependent documents. An SOP system is described as the entirety of all above-mentioned documents that include the processes to generate and alter, distribute, train, implement, and maintain them. One publicly available example is The European Medicines Agency's Integrated Quality Management System, which consists of six hierarchical levels, starting with the quality policy and the mission statement on level 1 down to "documents resulting from the process and needing to be controlled and stored in accordance with relevant agency policies and SOPs."[2]

A survey[3] conducted by a subgroup of the German Association of Research–Based Pharmaceutical Manufacturers (Verband Forschender Arzneimittelhersteller, vfa) has shown that in the pharmaceutical environment, the number of SOPs and related documents is increasing. There is no indication that the objectives, such as quality or efficiency of underlying processes, are achieved or improved this way. Also, there is a large variety both in size and structure of the SOP system across companies. The survey revealed that there are major deviations between what the SOPs describe and how processes are implemented in real life. Several hypotheses/questions should therefore be explored:

- Is there a lack of knowledge due to the large amount of SOPs that are produced and changed frequently?
- Is there a lack of discipline to adhere to SOPs?
- Are the SOPs simply inadequate, leading to the need for deviations?
- Are deviations tolerated actions to avoid major problems in these situations?
- Are SOPs too complicated to allow timely reactions to problem, thus procedural shortcuts are implemented?
- Are decisions not taken, although the process to arrive at them has been described in the SOP?
- Does management not care about supervising the execution and adherence of SOPs?

Within this survey, we learned that an ideal SOP system does not exist. Ways of thinking, expectations, and need for guidance differ considerably between functions. Experienced people require

broader margins for individual decisions while those with limited experience ask for more and stricter guidance.

The survey consisted of two sets of questions, one of which was directed to the management of clinical research, the other to the operations staff conducting the clinical trials (see charts at left and below; click on each to enlarge). In summary, the answers showed that this survey is a good starting point to generate ideas on how an ideal SOP system could look.

While we shall briefly discuss the characteristics of [6] ideal processes, the focus will be on the ideal SOP system—which requires that the individual processes are efficient by themselves. Regarding optimality, the requirements were, in summary, as follows ahead. It should be considered that there was a wide range of opinions, and this summary simply constitutes their majority. Our ideas on how to create an "ideal" SOP system are also vindicated by the results of the survey. The SOP system should cover all regulated processes, but only in a degree that allows optimization of processes easily.

'Ideal processes'

The definition of ideal processes is taken from business process excellence (e.g. ASQ[4], EFQM[5]). There, an ideal business process is seen both from the outcome and the necessary inputs.

Efficiency is defined as the optimal ratio of input vs. output. SOPs should reach their aim without the need to consume many resources. In fact, they should, through standardization, lead to fewer resources being consumed when achieving the same level of quality. Such questions could be answered by benchmarking with other organizations, or by consensus processes. It will be difficult in practice to find the minimum level of effort needed to achieve the necessary quality. In site monitoring, thresholds can be given; however, to transform this into an SOP is difficult, as there may be several different routes to arrive at this goal, and not all of them can be described in detail. Effort must be taken to measure efficiency in a reliable way in order to follow up on progress.

However, other criteria such as simplicity and adaptability have also been quoted. The following paragraph attempts, on the basis of experience, to develop a set of guiding principles. These will not be hierarchically ordered, however, some may carry more weight than others depending on the circumstances.

Guiding principles for SOP systems

1. Necessity/need

SOPs should only be defined where necessary. If they focus on rare situations, or situations which are not important for the quality of the study, they remain useless. Such situations should be managed depending on the circumstances of the individual case.

- Is the regulated process important?
- Is it frequently occurring?
- How often is it executed? Does it bear a significant risk?
- Is this quality level really needed?
- What would happen without regulated process?

An analysis should be performed as to which processes need detailed description and standardization for legal or regulatory reasons, which guides risks that need to be managed and to what degree, and whether SOPs are an adequate tool to do so. In some instances, the risks are minimal in comparison to the effort needed to avoid them.

Such a risk analysis describes the magnitude of risk, its probability of occurring, and the risk reduction through SOPs (and other measures) in two key dimensions: patient safety and data integrity.

In practice, the identification of processes without a need for an SOP is challenging. This is also reflected in the results of the survey that showed that "the vast majority was unable to identify SOPs that could be done without." In consequence, the focus should be on how detailed a process must be covered by an SOP and/or which process steps can be eliminated in order to achieve the needs of the different users/user groups.

2. Expediency/suitableness/effectiveness

Does this regulated process do what it is intended to do? This may also be called functional reliability or effectiveness. SOPs should be written in such a way that the objective of the underlying process is supported. One needs to avoid formal hurdles that hinder the objectives of the process being reached. One example is the reporting of serious adverse events (SAEs), where the need to report is more than obvious and the SOP, including any templates/forms, needs to provide an easy way as to how to best support the reporting. Every element, the SOP itself, the forms and the templates, needs to support a smooth reporting process and should not add problems to it.

Effective SOPs describe the processes in a way that their efficiency is not impaired by lack of clarity or understanding, and that they achieve the deliverables with a minimum of effort. Implementation of a new SOP, or SOP revisions should follow a pragmatic approach. If the need is there, implementation is more accepted by the users.

3. Simplification, transparency, and ease of acquiring

KISS—"keep it short and simple." An SOP should describe the standard situation of a process. Therefore, special rules and exceptions should be avoided. SOPs need not consider all imaginable situations. SOPs and associated workflows should be kept as simple as possible. As a rule, an employee should be able to easily memorize the relevant processes. Critical processes such as safety reporting should be easily available for everybody and everywhere. For less important processes or areas, an overview should be easily accessible for staff on

where to find the respective SOPs. To support easy access a logical and easy to remember numbering system can be of great help.

As an example, the EMA groups together documents according to their scope,[6] e.g.:

0001-0999 EMA (cross-agency)
1000-1999 PDM (Product data management)
2000-2999 INSP (Inspections)
3000-3999 H (Human)

4. Stability and predictability

"Less is more." Changes to SOPs should only be made for two reasons: if legal or regulatory changes mandate it or if major process improvements can be gained. Therefore, it may help to avoid detailed information, which are not process relevant but subject to frequent changes, for example, version numbers of supporting documents. In addition, highly variable elements, such as templates, may be attached to an SOP to be adapted without changing the SOP itself.

A regular review cycle of the SOPs (we suggest two to three years) should be established in order to evaluate whether modifications of processes or changes in the organization have taken place and are not covered by the SOPs.

5. Global reach

As almost all registration studies are multinational, SOPs need to be globally usable. Therefore, global SOPs should describe all globally defined processes to ensure harmonization and efficiency across the whole organization. However, regional or local amendments to global SOPs need to be possible but should only be introduced if required by regional/local law/regulations or organizational structures of affiliates.

Pitfalls of SOP improvements

1. Size of SOPs

There is an ongoing misconception that the size of SOPs is critical for the acceptance of the user. As we learned from the survey, more important than the size of an SOP or SOP system is how to navigate within and how the connections between them can be highlighted. This may explain why the satisfaction with the SOP system is not associated to its size.

2. Number of SOPs

Simplification of SOP systems often aims to reduce the number of SOPs based on the misbelief that the number is an important indicator of the quality and usability of the system. Respective activities are merging several SOPs into one document, renaming of SOPs to, e.g., working instructions, best practice documents, functional guidelines, and monitoring manuals. This is not the way to handle the problem, as the results of the survey pointed out that the number of SOPs does not matter at all.

3. 'Parallel SOP world'

There is a strong tendency to have, e.g., best practice documents outside of the official SOP system. This is born out of the misbelief that these documents are not in the scope of audits and/or inspections. According to ICH GCP, chapter 1.29,[7] the inspector can review every document deemed relevant.

4. Creation of a 'perfect SOP system'

SOP improvement projects almost always build on an existing system. They are adding further requirements and restrictions to already overregulated processes, with the aim of coming as close as possible to a perfect solution. Very often the current system is not questioned and, therefore, complexity is increased, slowing down changes, e.g., prolonged update cycles. PARETO rule (80:20)[8] should guide us also in this area.

5. Extent of SOP distribution

It is a misconception that distributing SOPs to a broader audience allows them to understand the big picture. This leads to an information overload, which can lead to frustration and resistance. The risk may be that relevant items are diluted by the vast amount of information.

6. SOPs do not 'stand alone'

The assumption that following the SOP ensures quality in itself is dangerous. The processes described in the SOPs need to be transferred into the individual daily business activities. It still requires lateral thinking and does not replace interactions and communications in specific situations.

7. SOPs do not claim the 'perfect solution'

The assumption that the SOP describes the perfect solution is misleading. The aim of an SOP is to provide a reliable, robust, and standardized way of reaching a defined outcome. "All roads lead to Rome."[9] There are always several potential routes to getting a result. The SOP defines one route for which we know how to manage hurdles and challenges.

8. Number of signatories

To ensure commitment and acceptance of SOPs, often all concerned line managers are included in the sign-off of the SOP during the release cycle. This is based on the assumption that signing an SOP increases acceptance and commitment of the user. Finally, it prolongs the release cycle and slows down the update of SOPs. Thus, the number of signatures should be minimized. Nevertheless, process modifications always have to be aligned with the relevant functions.

9. Can everyone write SOPs?

Writing an SOP is challenging and requires deep insight into how to analyze processes and how to describe and visualize them. The SOP system in its entirety should appear in a har-

monized and standardized format. Preferably an SOP writer is recommended, who acts as moderator and even as change manager during the SOP generation process.

Recommendations

1. Format of an ideal SOP

An SOP should follow the logical flow of a process and describe the associated roles and responsibilities. Flow chart(s) could provide an easy and quick overview. This can be implemented using business process modeling software, which can help identify shortcomings in the underlying process.

Any process step should have one responsible role that performs the activity. Further contributors can be visualized using a RACI matrix (R=responsible, this function does the actual work, A=accountable, this function supervises and decides; C=to be consulted; I=to be informed).[10,11]

If further governing or dependent documents are associated with SOPs, e.g., forms, templates, standard letters, related SOPs, checklists, or literature references, they need to be clearly referenced. Interfaces to other SOPs should also be mentioned. The interfaces may transgress the boundaries of a department, and may, therefore, have to be aligned with processes in other departments. Preferably a process should be described in one SOP only (end to end). If hyperlinks are used, the selection of the current version should be ensured to avoid outdated links. In addition, the SOP must contain transition rules, and version change details.

2. Who should write SOPs?

SOPs should be written by specialized/professional SOP writers who interview the process owners to translate the steps into a well-arranged process flow. Clarity, simplicity, and intuitive logic should guide them.

As alternative, specialized SOP facilitators (i.e., experts who support the subject matter experts) can be used when the process owners try to write the SOPs as they do it. In any case, the overall responsibility for the appropriateness of the business processes resides with the operating functions.

3. Implementation and training

Who should receive SOPs? Only persons that appear in the RACI chart as "R" (responsible: the one who does the work) or "A" (accountable: the one that supervises and makes decisions) should be recipients of respective SOPs.

Implementation of SOPs/updated SOPs always includes training and should therefore be reflected in the individual function training plans. The type of training is determined by complexity of changes and criticality of underlying processes. This can be self-reading (read and acknowledge), e-learning, web seminar, or face-to-face training. Training should be completed ideally prior the SOP coming into effect. However, the very latest point of training completion should be before the activity described in the SOP is performed by the individual. This needs to be documented and may be, for example, covered by a learning management system.

Independent from type of training, a plausibility check should be performed at least as to whether the training has been effective:

- In a web session or face-to-face meeting, the use of the TED system during training maintains anonymity but shows how much has been learned and what may be sources of misunderstanding.
- For online training courses, a quiz requiring a predefined success rate can be useful.
- For self-reading, the confirmation of 'read and understood' might be sufficient.

The overall training effect has to be supervised by the line manager to verify that the training positively influenced the daily business. Another option could be assessments some months after the SOP becoming effective.

4. Control of SOP adherence and continuous improvement

There are different approaches to validating and developing a system. From within the own organization, feedback and proposals of users will help as much as the thorough analysis of results from audits and self-assessments and quality checks, especially with regard to SOP violations. From external sources, the result from regulatory inspections as well as SOP violations by external partner (e.g., investigators) are noteworthy. In larger organizations, an electronic tracking system will become necessary.

In each instance, it is necessary to perform detailed root-cause analysis to differentiate, for example, between an inadequate process/SOP and an appropriate process/SOP but with major problems in training and discipline in adhering to the SOP. Use of the "five whys"[12] is often helpful in order to identify the underlying problems.

This information needs to be fed into a continuous improvement cycle (PDCA)[13] in order to optimize the SOP system.

Discussion and conclusion

Obviously, our project to achieve an "ideal" SOP system is very ambitious. We've learned from the survey that the majority of users feel SOPs are too extensive, too restrictive, and too complex. Nevertheless, at the same time, they consider SOPs useful, necessary, and satisfactory. Consequently, there are competitive endeavors and requirements in both directions of enlarging and reducing levels of detail of an SOP system (and a lot more actions). At the same time, nobody is willing or ready to waive a process or standard procedure. Thus, it seems that there is no easy fix.

Knowing that, we chose the basic approach to make efforts toward improving SOP systems more rational. It is the nature of continuous improvement that volume and complexity of SOP systems increases, because details are supplemented in order to comply, as a rule, with audit or inspection findings or

to implement more complex requirements. Most often we lack the courage and not only time and effort to redesign an operating process or the SOP system from scratch.

We are convinced that challenging our "improvements" with respect to necessity, effectiveness, clarity, simplicity, and reliability can help us to optimize our SOP systems pragmatically.

Sometimes we will reach the outer limits of the doable and sometimes only the courage to challenge the fundamentals of our systems will open new options.

Many of our ideas are characterized from the perspective of large sponsor organizations. But they may be transitioned also to smaller entities. A special case, and thus not reflected in our recommendations, may be so-called globally outsourced trials, where the definition of deliverables is advantageous when working with CROs that may have different processes. Time, cost, and quality should define the desired end result and ensure that legal and regulatory principles are not violated.

In addition, it may be considered even within an "own" SOP system whether a description of the deliverables (final state of outcome or quality level) should complement a precise description of processes in a SOP. In reality, a combination of both approaches may be needed. For instance, to make the degree of control of protocol deviations meaningful, the allowable percentage of major and minor deviations could be described.

The SOP system should always be part of a quality management system. Therefore, also structurally, other means of assuring and promoting quality should always be considered. The development and use of SOPs should be aligned with all those other processes, such as audits and inspections, quality management reviews, and self-assessments. Ideal SOP systems require that their use is not associated with information overload and complexity, as this will cause an increase in errors. Therefore, some principles have been described, which can be checked against when changes in the "own" SOP system have been contemplated. Finally, an ideal SOP system is ideal at a certain point in time, and needs constant renewal to stay like that.

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*In memoriam: This article is dedicated to the memory of Dr. Michael Herschel (1953-2014), who initially chaired the team of authors.

References

1. The Ideal SOP, Posted on: 09 Feb 09, Jo Hills - Field Reporter, retrieved July 15, 2015; [cited 2015-Dec-03] available from http://www.pharmiweb.com/Features/feature.asp?ROW_ID=1156&channel=3
2. The European Medicines Agency's Integrated Quality Management System POLICY/0001 EMEA/MB/355781/2007 Rev.1; 10-MAR-2009
3. Gabriele Schmidt, D. Baier, Arthur Hecht, and M. Herschel, SOPs in Clinical Research, Applied Clinical Trials July/August 2013. http://www.appliedclinicaltrialsonline.com/sops-clinical-research
4. ASQ - American Society of Quality [cited 2015-Dec-03]. Available from http://www.asq.org/index.aspx
5. EFQM - European Foundation for Quality Management [cited 2015-Dec-03], available from http://www.efqm.org/
6. Creating and maintaining SOP/WIN folders in EDMS WIN/EMA/0035, 09-Jul-2010
7. ICH Harmonized Tripartite Guideline, Guideline for Good Clinical Practice E6 (R1), current step 4 version dated 10-Jun-1996 [cited 2015 Dec 03]. Available from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
8. According to Vilfredo Pareto [12] (1848–1923) [cited from Wikipedia 2015-Dec-03] ; Pareto, Vilfredo; Page, Alfred N. (1971), Translation of Manuale di economia politica ("Manual of political economy")
9. McGraw-Hill Dictionary of American Idioms and Phrasal Verbs, © 2002 by The McGraw-Hill Companies, Inc.
10. Smith, Michael L., James Erwin, and Sandra Diaferio. "Role & responsibility charting (RACI)", abgerufen am 17 (2007): 2007, [cited 2015-Dec-03] available from http://www. pmforum.org/library/tips/pdf_files/RACI_R_Web3_1.Pdf
11. Morgan R. How to do RACI charting and analysis: a practical guide, 22-Sep-2008 [cited 2015-Dec-03] available from https://www.projectsmart.co.uk/how-to-do-raci-charting-and-analysis.php
12. Duke Okes: Root Cause Analysis: The Core of Problem Solving and Corrective Action, 2010
13. Deming, W.E.: Out of the crisis. Massachusetts Institute of Technology, Massachusetts, USA, 1986