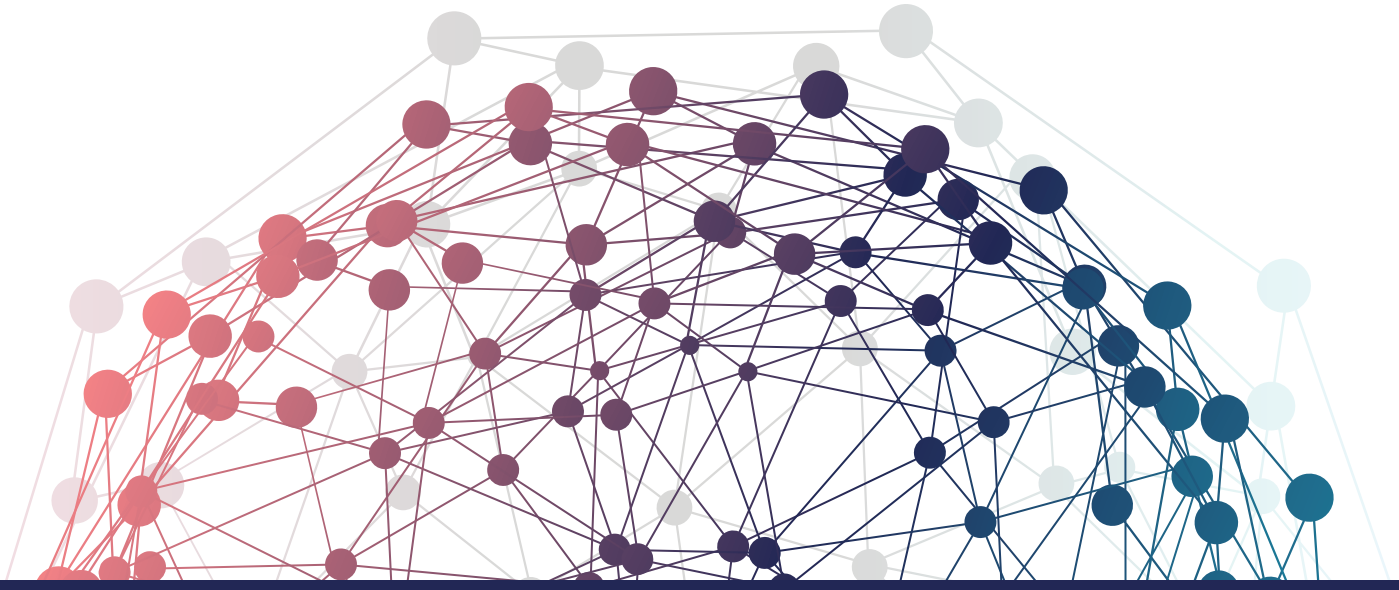
EXECUTIVE SUMMARY

THE AVOCA GROUP

QUALITY CONSORTIUM SUMMIT 2014

Progress through Collaboration —
Breaking Down Silos, Advancing Technology,
and Building Bridges to Patients

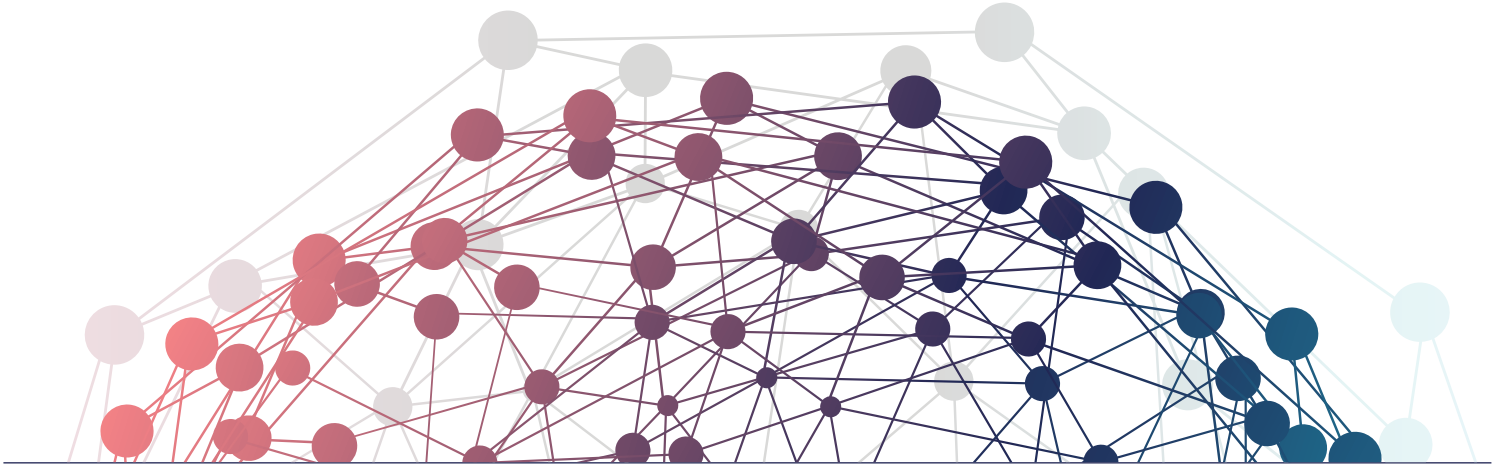


May 6-7, 2014
www.theavocagroup.com @AQCSummit2014

The Avoca Quality Consortium Summit, held May 6-7, 2014, in Princeton, NJ, was the Third Annual meeting for The Avoca Quality Consortium, a cooperative effort that brings together quality, outsourcing, and operational professionals from Member pharma, biotech, clinical service providers, and CRO organizations to accelerate the development of a best-practice approach to quality management and CRO oversight.

Currently, the The Avoca Quality Consortium includes 34 Members: 21 pharma/biotech companies, 12 Contract Research Organizations, and 1 clinical service provider. The corporate sponsors of the Quality Consortium are Eli Lilly and Company and Pfizer, Inc.

Special thanks to our Executive Summary Sponsor, inVentiv Health Clinical.



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About The Avoca Quality Consortium

Founded in December 2011, The Avoca Quality Consortium is a membership fee-based consortium designed to help sponsors, CROs, and clinical service providers optimize their approaches to proactive quality management with an emphasis on bringing them into greater alignment.

The mission of the Consortium is to serve as a catalyst for the acceleration of best practices and industry standards for proactive quality management and risk mitigation.

According to Patricia Leuchten, Avoca's President and CEO, "We know that sponsor companies are striving to become more efficient in the oversight of CROs and are striving to reduce the duplication of effort while focusing on maintaining very high quality. Eliminating the duplication of effort requires collaboration on a higher level. The work of The Avoca Quality Consortium is to bridge gaps and serve as a vehicle for developing mutually agreed upon leading practices for quality." Avoca is using its industry and Consortium Member research survey data, consultants, subject matter experts, and partners to set strategic direction and to rapidly develop these industry best practices.

About The Avoca Group

Founded in 1999, The Avoca Group Inc. is a leading integrated research and consulting firm based in Princeton, New Jersey. The Avoca Group develops and implements global relationship and alliance management programs for pharmaceutical companies, biotech companies, and pharmaceutical service providers.

Avoca helps clients build, measure, and manage critical business relationships. Avoca's clients include the top five pharmaceutical companies and global contract research organizations as well as small companies seeking aggressive growth within the healthcare industry.

The Avoca Group Inc. conducts industry research on trends in clinical outsourcing each year, presenting the results, *The Avoca Report*, at international conferences and via industry publications. The Avoca team consists of pharmaceutical industry veterans and subject matter experts in the areas of large scale organizational change, relationship management, and survey research.

THANK YOU TO OUR 2014 SUMMIT GOLD SPONSOR

ICON plc is a global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries. The company specialises in the strategic development, management and analysis of programs that support clinical development - from compound selection to Phase I-IV clinical studies. With headquarters in Dublin, Ireland, ICON currently, operates from 76 locations in 37 countries and has approximately 10,300 employees. Further information is available at www.iconplc.com.

THANK YOU TO OUR 2014 SUMMIT SILVER SPONSORS

Acurian is a leading full-service provider of clinical trial patient enrollment and retention solutions for the life sciences industry. The company increases the enrollment performance of investigator sites worldwide by identifying, contacting, pre-screening, and referring people who live in the local community but are unknown to a research site. As a result, trial sponsors complete enrollment without incurring the unexpected expense of adding sites, time, or CRO change orders.

DrugDev streamlines engagement among sponsors, CROs and doctors to advance the common goal of doing more trials. Through the creation of global, standardized processes, the use of smart technology, and the cultivation of unique relationships DrugDev is consistently and efficiently transforming the way drug developers identify, engage and pay investigators.

INC Research is a therapeutically focused contract research organization with an unrivaled reputation for conducting global clinical development programs of the highest integrity. Pharmaceutical and biotechnology companies look to INC Research for a complete range of customized Phase I-IV programs in therapeutic areas of specialty, and in innovative pediatric trials. Our “Trusted Process™” methodology and therapeutic foresight leads our customers to more confident, better-informed drug and device development decisions. For more information, please visit our website at www.incresearch.com.

inVentiv Health Clinical is a leading provider of global drug development services to pharmaceutical, biotechnology, generic drug, and medical device companies, offering therapeutically specialized capabilities for Phase I–IV clinical development, bioanalytical services, and strategic resourcing from a single clinical professional to an entire functional team. With 6,500 passionate employees supporting clients in more than 70 countries, inVentiv Health Clinical works to accelerate high quality drug development programs of all sizes around the world. www.inventivhealthclinical.com

2014 MEMBERS OF THE AVOCA QUALITY CONSORTIUM

*associate member

Dear Avoca Quality Consortium Colleague,

Pharmaceutical and biotech sponsor leaders continue to pursue more efficient and effective approaches for the oversight of CROs and niche clinical service providers to reduce the duplication of effort while maintaining or enhancing quality. In parallel, CROs are continually elevating their levels of quality and desire solid partnerships with sponsors without the heavy burden of micromanagement. In December 2011, Avoca established the Avoca Quality Consortium (AQC) to create a forum for sponsors and CROs to come together in collaboration in order to develop more consistent and effective approaches to the proactive management of quality within outsourced trials.

Since its inception, the AQC has successfully bridged gaps and developed mutually agreed upon best practices for quality and leading practices to pave the way for improved outcomes. These best practices are improving processes for clinical programs and are enabling more effective long-term strategies and more integrated, intuitive approaches for relationship building and partnering between sponsors and CROs, as well as other clinical service providers.

Now that our Third Annual Quality Summit has concluded, we can appreciate how far we have come since the Consortium's inception in 2011. In the past two and a half years we have:

- Engaged the industry in clarifying and incorporating efforts and uptake on the utilization of clinical Quality by Design best-practice tools in order to focus on errors that matter and effective risk decision management.
- Developed a standard, modularized quality agreement template for sponsors and CROs to use to ensure clarity, understanding and alignment on expectations for outsourced work.
- Developed a core set of quality metrics, and donated output to the MCC.
- Created a framework for quality oversight and proactive quality management of outsourced programs, completing the majority of the eight best-practice component swim lanes, with the remaining components to be finished this year.
- Conducted industry research regarding prequalification and routine system audits of full-service CROs and niche providers.
- Progressed with the prequalification project using a phased implementation approach, having presented a formal proposed path forward based on the advisory panel's recommendation.
- Collaborated with The Society of Clinical Research Sites (SCRS) on a survey to gather sites' feedback and opinions about quality management practices and sites' perceptions of sponsors and CROs.
- Presented a taxonomy for the assessment, reporting and utilization of quality-based metrics, with a proposed benchmarking study that will evaluate actionable variables that impact the quality outcomes for clinical programs.

- Reported on annual Consortium Member benchmark survey research:
    - 2012: Approaches to proactive quality management and effective oversight
    - 2013: Risk assessment and risk management
    - 2014: Quality management practices
- Brought industry executives and experts together through face-to-face industry leading Quality Summits and Working Sessions as well as educational webinars to share best practices and to engage in the development of industry leading practices.

Every year, we redefine our goals and initiatives for the Consortium based on Member feedback to reflect the changing business and scientific environment in which we live. In 2014 we have delivered on a number of exciting initiatives based on your input, and will continue to deliver more as the year progresses.

We are proud to have had the participation of the industry's best, brightest, and most engaged clinical leaders from sponsors and clinical service providers alike, working in clinical development and quality. We thank all of the Members for their participation in the interactive discussions and in choosing to engage in a forum to find proactive approaches to the fundamental challenges being faced by the industry.

We hope you walked away from the Summit inspired to be agents of change within your organizations to improve quality and efficiency of clinical development.

We are pleased to present this recap and overview of the 2014 Avoca Quality Consortium Summit and thank inVentiv Health Clinical for sponsoring the report and enabling us to share these highlights with you. Thank you to everyone who made this year's Summit such a memorable success and we look forward to working with you throughout the year!

Warm Regards,

STEVE WHITTAKER
Avoca Quality Consortium
Executive Director
The Avoca Group, Inc.

PATRICIA LEUCHTEN
President & CEO
The Avoca Group, Inc.

> "Individual commitment to a group effort — that is what makes a team work, a company work, a society work, a civilization work."
>
> – Vince Lombardi

OPENING REMARKS FROM THE SUMMIT CHAIR

DR. JEFFREY S. KASHER
Vice President, Clinical Innovation and Implementation, Eli Lilly and Company

Jeffrey S. Kasher, Ph.D., was named Vice President, Global Clinical Innovation and Implementation, in September 2012. In this role Jeff has the opportunity to lead significant, disruptive, Patient Centric Transformational efforts in the company and ensure delivery of the innovative molecules that are currently in Lilly's clinical portfolio.

Dr. Kasher received a Bachelor of Science degree in chemistry from Franklin & Marshall College (Lancaster, PA), a doctorate in pharmacology from the State University of New York (Syracuse) and a postdoctoral fellowship in physiology at Yale University School of Medicine.

Dr. Jeffrey Kasher welcomed everybody to the Avoca Quality Consortium Summit's third annual meeting and set the tone by posing a critical question to attendees:

How do we get an industry that is so slow to change to improve the clinical trial enterprise?

"All of us are in the business of developing innovative medicines to allow patients to have longer, healthier, more active lives. The Avoca Quality Consortium is part of this movement in the last three to four years, where companies in common business sectors come together to work on things in a pre-competitive space. So, why are we all here?" Kasher asked.

As outsourcing models change there is more work that needs to be done to enhance how sponsors partner with CROs. Although much progress has been made, a significant opportunity remains. This year, the Avoca Quality Consortium is working on major initiatives, including the prequalification of niche service providers, Quality by Design (QbD), and reducing errors that matter. And although we are still in this together and making progress, patients just don't have time to wait.

Kasher shared that less than 5% of doctors participate as investigators in clinical trials, and less than 5% of patients participate in trials. He noted that these two groups should be more involved in industry discussions. Kasher believes there is an opportunity to more actively involve sites in order to dramatically improve how the industry conducts clinical research. Patients should also be engaged for input into clinical trial design, to identify barriers in the conduct of trials, and for other needs that Kasher says "the pharmaceutical industry has been talking about but still is slow to act upon."

The end goal is to reach the point where we can get medicines to patients more rapidly than we can at present.

"Patients are putting their lives on the line in the name of clinical research, and we owe them that at a minimum," Kasher stated. "If we continue to build on what we have done in the Avoca Consortium Quality, I believe we CAN get medicines to patients more rapidly than we do today. My hope for this meeting is that everybody leaves here with a new idea or confirms an idea to take back to where you work and apply it, and in doing so, make you and your organization a bit better at accelerating medicines to patients."

EVENT HIGHLIGHTS & TESTIMONIALS

"All of us are in the business of developing innovative medicines to allow patients to have longer, healthier, more active lives. The Avoca Quality Consortium is part of the movement in the last three to four years where companies in common business sectors come together to work on things in a pre-competitive space."

– Dr. Jeffrey S. Kasher, Vice President, Clinical Innovation and Implementation, Eli Lilly and Company

"The Status Quo Sucks."

– George Carlin

"There is power in this group to change this industry."

- Coleen Glessner, Vice President, Head of Clinical Trial Process & Quality, Pfizer, Inc.

"Culture and transparency are huge roadblocks to transformation of healthcare. And that is beginning to happen."

- Jeff James, CEO, Wilmington Health, Inc.

"We are entering a fourth era of computing: the era of smart computing. That is optimization. Smart computing will help us make smarter, better, decisions."

– Steve Sashihara, President and CEO, Princeton Consultants Inc.

"The future of our industry depends on our ability to effectively engage patients."

- Patricia Leuchten, President and CEO, The Avoca Group, Inc.

BRIDGING TOWARDS A COLLABORATIVE PATIENT-CENTERED FUTURE

JAMIE HEYWOOD
Co-Founder, PatientsLikeMe

Jamie Heywood is one of the foremost practitioners using technology to transform the future of healthcare. Jamie is a leader in engaging patients, understanding their needs and in applying entrepreneurial smarts and drive to improving the treatment and delivery available to them. He is a passionate believer in transparency and collaboration. As the founder of PatientsLikeMe — an innovative web community that allows patients to pool their experiences of disease and treatment — Jamie took an innovative, bottom-up approach to both patient support and medical research. It's a groundbreaking approach that is speeding up the pace of research, democratizing patient data, and improving the dialogue between patients and physicians.

In addition to founding PatientsLikeMe, Jamie is also the founder of ALS Therapy Development Institute (TDI), the world's first non-profit biotechnology company. He founded the company following his brother Stephen's diagnosis of ALS (Lou Gehrig's disease) in 1998.

Jamie Heywood presented a provocative, passionate, and inspirational keynote presentation at the 2014 Avoca Quality Summit on the topic of "Subjects No More — Will Your Trial Meet the Patients' Eligibility Requirements? Bridging to a Collaborative Patient-Centered Future."

He commenced by providing the audience with the background of the PatientsLikeMe web community, and the genesis of the idea for what he originally envisioned as a "dating site for patients" that would include a large range of measurements that patients would record about their personal experiences.

The web community currently has more than 250,000 patients with varying conditions. Participants log the progress of their disease in very fine detail, including their treatments and prescriptions, any side effects they experience and much more. This has two consequences. First, patients can look at others' logs and even message one another to learn about the real-world experiences of patients like themselves. Secondly, this creates a treasure trove of data about a wide range of illnesses and treatments far beyond what can be captured in traditional clinical studies.

Jamie highlighted the value of focusing on the patient experience and emphasized that pharmaceutical, biotech, and CRO organizations would benefit from truly understanding that the patient is seeking health and wellbeing and that the clinical trial process is only a thin sliver in the overall scheme of a patient's experience with a disease. Jamie noted that the pharmaceutical industry has largely ignored the formative stages of a patient's life, including events prior to a trial; as well as what happens to a patient after they leave a clinical study.

"This is a missed opportunity, because there is a lot of information that we aren't storing, outside of a clinical trial, and those data just dissolve outside. Therefore we are continuously rebuilding the system." Furthermore, Jamie stated that this is "ripping off" patients who have put their lives on the line, especially given that data is not passed along to improve the next clinical trial. He emphasized that patients should be treated like partners, and patient follow-up post-trial is in dire need of improvement.

Jamie noted a commonality between patients and pharmaceutical companies in that they are deeply aligned in their desire for innovative treatments. "Patients are desperate for help, and will do it any way they can. They can be your partners. I see the beginning of a learning system, which if adapted to and connected to in the right way, can help build a future faster."

BRIDGING TOWARDS A COLLABORATIVE PATIENT-CENTERED FUTURE

Jamie challenged executives to, "Ask not what patients can do for you but what you can do for patients."

Jamie discussed the value of patient-centered drug development that measures and manages impactful health, which is not the same thing as what is recorded through electronic medical records. Jamie defines patient-centered development as measuring meaningful variables that impact an individual's health. He defines human-centered as something that is clear, answerable, efficient, relevant, educational, harmless, and actionable to the patient. Jamie refers to this impactful health as health that uses the patients' language and is medically validating.

"We live in a world that is wired, and people measure their health information. So there is a plethora of information, cognitive assessments, etc. contained in that environment within the context of a trial. We just have to figure out how to capture it."

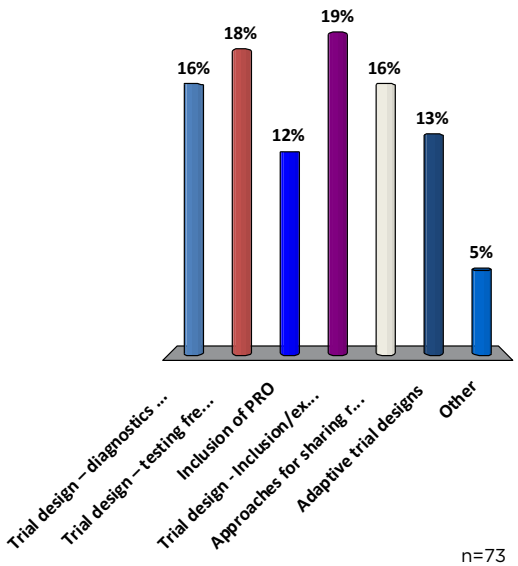
An audience member commented that, although conceptually, bringing in the patient as a partner makes sense and is necessary for the pharmaceutical industry, there is often internal, organizational resistance to this type of change until it somehow translates to true value by providing results in shortened timelines, more effective protocols, or higher retention rates. Therefore, the challenge becomes proving that bringing in the patient perspective translates to real results in improved clinical trial outcomes.

But Jamie's presentation brought up issues beyond bringing in the patient voice to optimize drug development processes; it probed a highly competitive and regulated industry to consider how to allow information to have a greater role, in a pre-competitive way, in shared learning to change the healthcare system and improve treatments for disease.

Poll taken at the Summit

How could patients' data best impact trials? (Select all that apply)

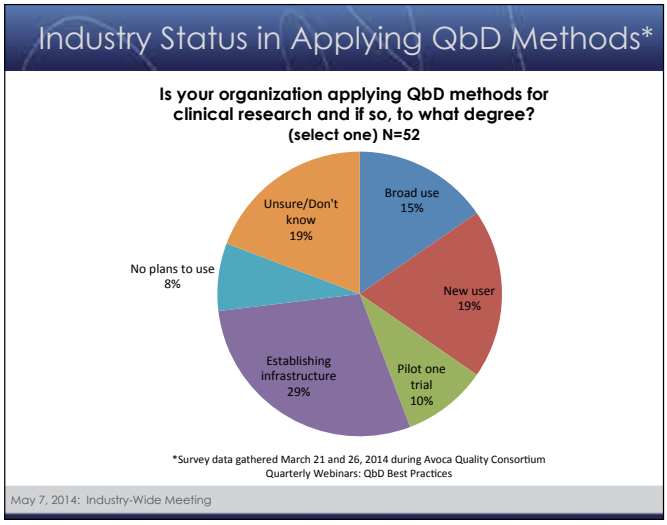
A. Trial design – diagnostics tests
B. Trial design – testing frequency or complexity
C. Inclusion of PRO
D. Trial design - Inclusion/ exclusion
E. Approaches for sharing results
F. Adaptive trial designs
G. Other

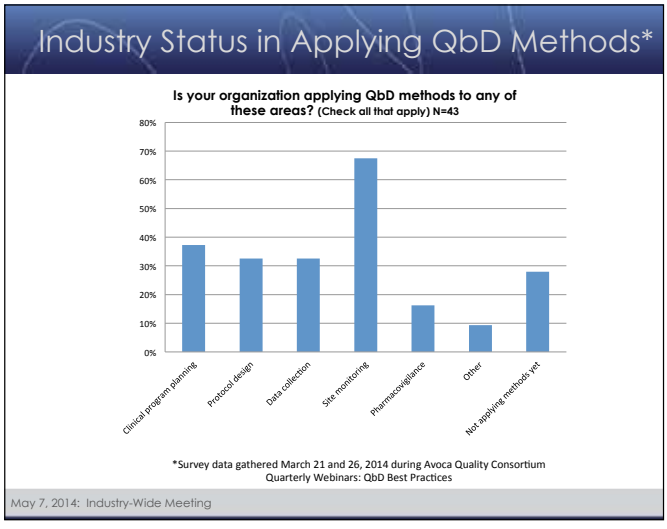


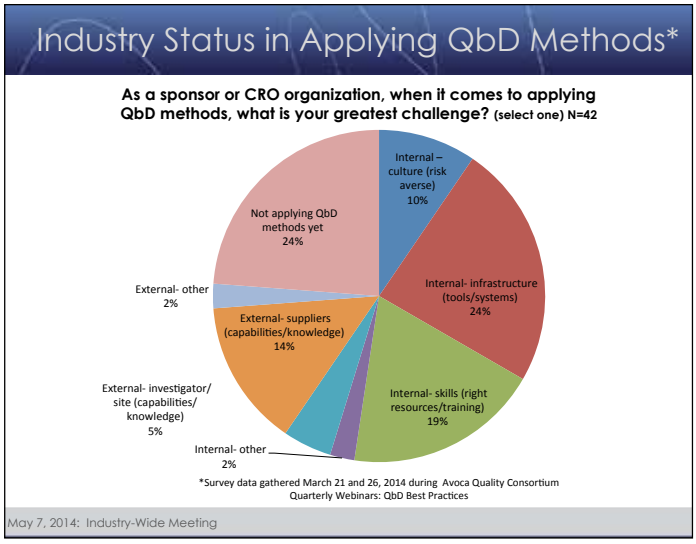
QUALITY BY DESIGN (QbD) – IMPLICATIONS FOR PROTOCOL DEVELOPMENT AND CLINICAL OPERATIONS WITHIN PARTNERED OUTSOURCED PROGRAMS

Janis Hall, Senior Consultant, The Avoca Group, provided attendees with an overview of some of the Avoca Quality Consortium data that were collected to assess what the industry is doing to build quality into clinical trials, and the industry's current use of these Quality by Design principles.

Only approximately half of the respondents stated that they had at least a "good understanding" of QbD processes, as applied to clinical development. CRO respondents were more likely than sponsor respondents to report frequent or consistent application of QbD principles in clinical development, but sponsors don't appear to be aware of CRO's application of these approaches.







The pharmaceutical industry has historically been a risk-averse industry, but one of the keys for success is to identify the errors that matter and prevent them from occurring. In order to effectively implement QbD approaches with outsourced partners, CROs and Sponsors should:

- Assess suppliers for knowledge, experience and expertise implementing QbD methods
- Deploy best practices for conducting supplier risk assessments for outsourced services
- Collaborate with partners to ensure appropriate implementation of QbD processes
- Build QbD methodologies into vendor contracts

The new approach is a win for the industry as it is practical and sustainable, contains cost, improves quality, increases safety, improves data integrity, and could help drive more quality submissions which can lead to more product approvals.

A panel of executives was asked a variety of questions related to the Quality by Design impact on the absence of errors that matter and risk management.

QUALITY BY DESIGN (QbD) – IMPLICATIONS FOR PROTOCOL DEVELOPMENT AND CLINICAL OPERATIONS WITHIN PARTNERED OUTSOURCED PROGRAMS

Coleen Glessner, Vice President, Head of Clinical Trial Process and Quality, Pfizer, Inc., shared her thinking in three words: Plan. Control. Improve.

"You can plan to have a system that will prevent quality issues via alert notifications, or it can be a standard operating procedure that lays out expectations with regards to audits, inspections and telling you when something is wrong so you can have the opportunity to fix it. The fear factor from regulations can drive behavior to enable compliance, but it does not drive quality. It will take a culture change to drive quality. In the industry, we are moving from an emphasis on compliance to the regulations to an emphasis on building in quality from the start."

Glessner referenced the FDA Guidance document issued August 2013 on risk based monitoring, which shares risk assessment and management approaches that can drive quality. She also mentioned the importance of getting the protocol right and building integrated risk mitigation plans. Improved strategic partner alliances and vendor oversight are also key in building in quality for clinical trials.

Dr. Peter Aurup, Vice President and Head, Global Trial Operations, Merck Research Laboratories, commented that the industry is constantly chasing the moving target of expectations of what quality looks like- internally, in emerging regions, and from regulators. He believes regulators need to articulate the expectations around quality aspects of clinical programs.

Aurup discussed the challenge of increasing protocol complexity, and referenced a 2010 article from Tufts on this topic. "Although a lot of progress can be made inside organizations in how they are thinking of and designing protocols, an external perspective and input is important. We need to sit down with sites and have some understanding of how those protocols work within standard of care."

Dr. Stephen Cutler, Group President, ICON plc, stressed the importance of having regulators be partners in these discussions. He also noted that while you can measure all sorts of metrics, the true work is in what you do if these measures go off track and how you intervene to make sure you get a clinical program back on track.

Dr. Jeffrey S. Kasher, Vice President, Clinical Innovation and Implementation, Eli Lilly and Company, commented that the "essence of getting this right is Quality by Design, with the key word being 'design'." He shared that at Eli Lilly, they went after protocol amendments within the first 100 days, and wanted to take out avoidable amendments such as process errors, quality errors, and even new information.

"If we have a protocol amendment in a Phase III study, prior to first patient in, that means the work upfront was not done adequately," Aurup commented.

Yet sometimes the challenge lies in getting people to "think differently" within their organizations and/or with partners. Glessner mentioned her belief that investing in the culture to think differently on quality and compliance is key. This could include training, events, and workshops on Quality by Design, so that everybody within the company feels ownership in the project that ultimately resulted in the potential launch of new medicinal products. People need to feel accountable and see quantifiable progress.

She says, "We don't talk about quality as a strategic competency that differentiates our businesses from each other. It is rare to hear a corporate strategy with a pillar of quality. I think that this is the biggest lever for changing the way we work. **There is nothing we shouldn't share to progress quality in our industry**."

> "Alone we can do so little: together we can do so much."
>
> – Helen Keller

INSIGHTS ON QUALITY AND EFFECTIVENESS

JENNIFER BYRNE
CEO of PMG Research

Jennifer Byrne, CEO of PMG Research, leads one of the largest Integrated Site Networks in the U.S, which provides a comprehensive research infrastructure to large multi-specialty physician practices, healthcare institutions, academic centers, and community based private practice physicians. Jennifer and her team of 150 Clinical Research Coordinators and support staff and 130 Principal Investigators have conducted over 7,000 pharma and device trials with the inclusion of well over 100,000 trial participants. She is the founder of The Greater Gift Initiative, a non- profit organization dedicated to honoring clinical research volunteers through the gifting of lifesaving vaccines to children in developing countries. Jennifer serves on the Advisory Board for CISCRP and the Wake Forest Institute for Regenerative Medicine, and has served as Mentorship Committee Chair for the Society of Clinical Research Sites. Jennifer was named to the CenterWatch Top 20 Industry Innovators in 2013.

JEFF JAMES
CEO of Wilmington Health

Jeff James is the CEO of Wilmington Health in Wilmington, NC. He is responsible for the strategic vision and its deployment as well as all financial and operational aspects of the practice. Jeff is a frequent national speaker on a diverse range of subjects including: Lean/Process Improvement in Healthcare, Cultural Transformation, Aligning Incentives and Physician Leadership. He is a physician advocate and healthcare executive with over 18 years of strategic and operational experiences. He has participated as an active Board Member on several community and healthcare related organizations including: The American Medical Group Association, Coastal Connect Health Information Exchange, the Economic Development Corporation, Wilmington Chamber of Commerce and the North Carolina State Medical Society's ACO Steering Committee. Jeff holds a Master of Business Administration Degree and is a Certified Public Accountant.

IBRAHEEM MAHMOOD
President & CEO of DrugDev

As President and CEO, Ibs Mahmood defined the DrugDev vision: to provide technologies and services to clinical trial doctors that allow the pharma industry to conduct trials faster, smarter and cheaper. His strategy to deliver this vision has been to build a world-class team backed by an outstanding investor base. Since joining in 2011, Ibs oversaw the growth of the company from just a handful of people to an estimated 200+ by the end of 2014; he and his team also raised an initial $50m investment from Invesco Perpetual.

INSIGHTS ON QUALITY AND EFFECTIVENESS

Jennifer Byrne and Jeff James provided a joint presentation on the topic of quality and effectiveness from the clinical research sites' perspective, delivering insights toward effective, quality-based site engagement.

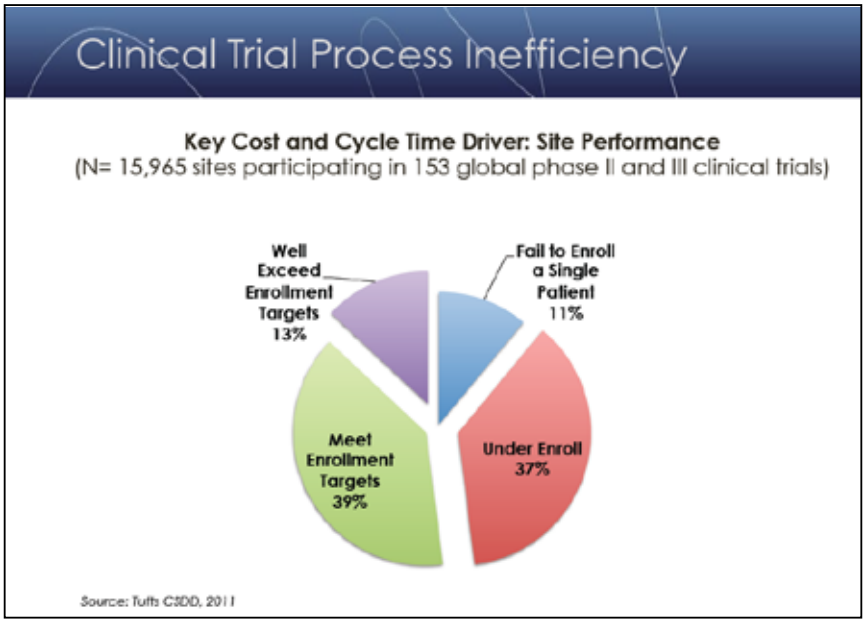
They noted some interesting clinical research statistics highlighting that while less than 1% of the US population participates in clinical trials, and 72% of patients say it's likely they would participate in a clinical trial if recommended by their doctor, only 22% say a doctor or healthcare professional ever talked to them about medical research. Healthcare providers have an immense opportunity to build awareness and grow participation simply by talking to more patients about clinical research.

Jeff James talked about the changing landscape in the healthcare industry that is both challenging and exciting. "The healthcare provider landscape is changing and the models and integration of clinical research with patient care is changing with it," he said. The diversity of the "site" model was presented, in which patient and pharma choices include freestanding research sites, academic/ community hospitals, single specialty practices, organized systems of care, and general practices.

Byrne and James hypothesized that a true model of clinical research integrated with an organized system of care illustrates a positive impact and notable separation in key study performance indicators and quality measurements. In response they introduced the idea of clinical research as a standard to improve quality of care.

The team showcased a case study that demonstrated a potential reduction in cost of care to the traditional payer through the inclusion of patients in clinical research studies. Furthermore, they presented a case study on patient experience that hypothesized that patients who are included in research would have a higher level of patient satisfaction and engagement than the overall population of patients.

Byrne concluded the presentation by summarizing several untapped opportunities and presented a variety of ways that the industry could benefit from improved key metrics and quality. These include: lower screen failure rates, more effective pre-screening and screening resulting from the identification of the right patients earlier in the trial process, increased randomizations and higher retention rates. Additional potential advantages cited were lowered cost for overall patient care, increased patient satisfaction, and increased demonstrable quality and improved population health.



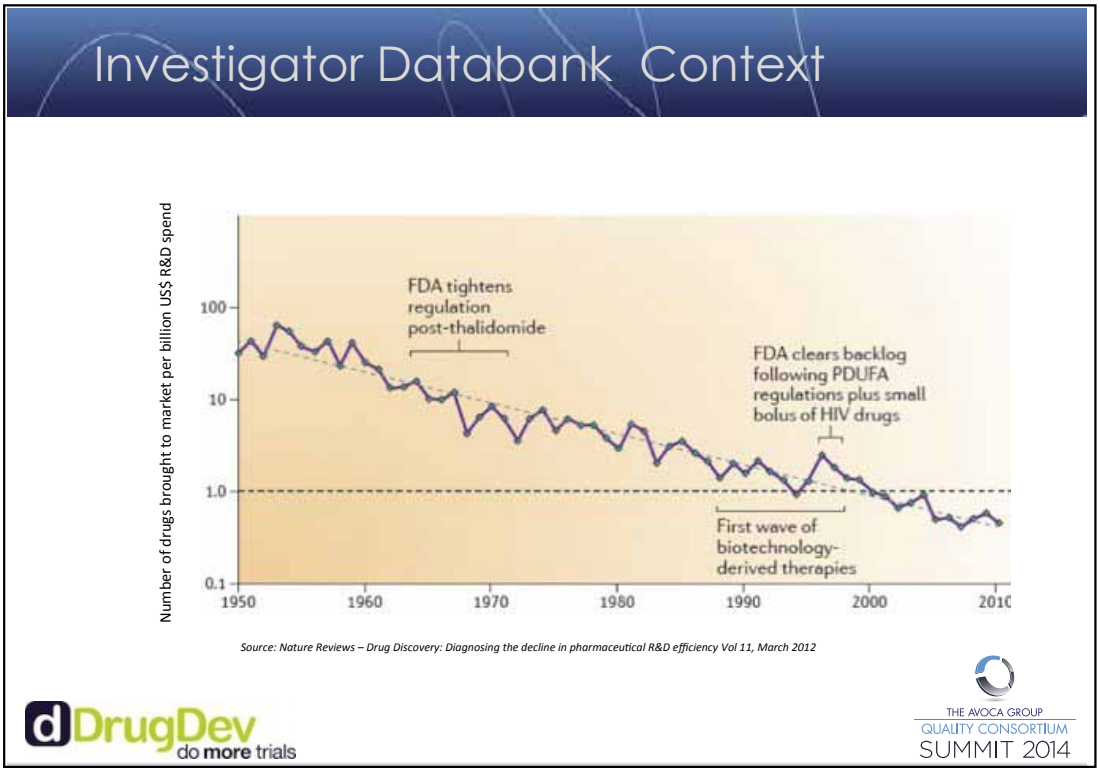
INSIGHTS ON QUALITY AND EFFECTIVENESS

Ibs Mahmood, President and CEO of DrugDev followed Byrne and James' joint presentation by sharing a personal story of him as a 13-year old boy. He described himself as immersed in technology since an early age and he developed the computer code that organizes the search function in a PC computer. This code was bought by Microsoft for $10,000, even though Ibs was offered a royalty deal, which he regrettably didn't take. "I was a young boy, and went to buy a bike." He told his personal story to emphasize that during that time, the computer industry was trying to change direction the same way that the clinical trials industry needs to change direction to address inefficiencies.

The lesson Ibs had learned was this: You need three things in order to change an industry. First, you need an idea. Secondly, you need to have a willingness to take a risk. Thirdly, you need quality.

Ibs believes that the heads of clinical operations, such as the executives in attendance at the Summit, need to be allowed to invest ahead of the curve. There needs to be enough cash and time to allow them to try new things. "We can't buy into this whole clinical trial complexity thing. The industry is decades behind. We need to be willing to work together to drive standards."

This concept was the genesis of the Investigator Databank. The Investigator Databank is a global collaboration between Janssen, Lilly, Merck, Pfizer and Novartis, to share investigator information for the benefit of both industry and investigators where they share investigator information in a collaborative and pre-competitive way.



THE OPTIMIZATION EDGE: REINVENTING DECISION MAKING TO MAXIMIZE YOUR COMPANY'S ASSETS

STEVE SASHIHARA
Co-founder and CEO, Princeton Consultants Inc.

Steve Sashihara is the co-founder and CEO of Princeton Consultants Inc., which blends information technology and management consulting. Steve leads the firm's Custom Optimization practice—transforming businesses by designing and installing software that makes tangible recommendations for action. Steve is the author of "The Optimization Edge: Reinventing Decision Making to Maximize All Your Company's Assets" (McGraw Hill), the first non-technical book to explain optimization to the busy business executive (www.optimizationedge.com). Steve graduated in 1980 from Princeton University. He serves on the advisory council for the university's department of Operations Research and Financial Engineering (ORFE).

Steve Sashihara opened the session by sharing 2002 Nobel Memorial Prize in Economic Sciences recipient Daniel Kahneman's philosophy that human beings are wired to have consistent, systematic biases in how we interpret data and make decisions, called an "anchoring bias", which inevitably has implications for our businesses.

According to Kahneman's theory, "An organization is a factory for producing decisions. Decisions are the most important product, so we should be thinking of a decision like any other product and apply quality controls to improve the quality of our decisions."

Sashihara stressed the importance of this because it is the decisions an organization makes that drive its performance. The inputs are data and the outputs are decisions and performance. A statistical model researched by Prof. Erik Brynjolfsson at MIT showed companies that adopt data driven decision-making gain 5-6% higher productivity and return on investments and asset utilization.

However, decisions are made from information, not data. Information is what essentially drives better decisions and in order to change data to information for improved decision-making, companies need to effectively utilize analytics. This includes descriptive analytics, predictive analytics, and prescriptive analytics in order to achieve optimization, which is defined as doing things faster and better.

Sashihara explained that optimization software allows decision-making using a special kind of software that can evaluate billions of combinations of possibilities and then provide explicit recommendation for action. This should be used instead of traditional decision-making without optimization that only considers a small number of choices.

"We are entering a fourth era of computing, the era of smart computing that is optimization. Smart computing will help us make smarter, better, decisions."

Optimization decision-making can be used for any part of an enterprise organization. Sashihara left the audience with some practical valuable tips for how to bring optimization into their organizations:

- Conduct an Optimization Opportunity Assessment; choose an asset and a decision area, analyze how decisions are made today, and quantify optimization potential upside.
- Get an outside perspective to reduce biases in analyzing decision making
- Quantify the optimization potential: Take a data snapshot and see the potential upside of improving this decision
- Find an objective function and assess how a process is being done today. Identify what you are trying to accomplish. Create a proxy for how you decide on a tricky issue.
- Take a "hard" case and see if they can split it into two scenarios. Identify what variables you could extract that could help you make a better decision

You don't have to be a specialist in optimization in order to solve problems with optimization.

FIRST FOLLOWER: LEADERSHIP LESSONS FROM DANCING GUY

During the first day of the Avoca Quality Consortium Summit, a 3-minute YouTube video was shared to provide lessons on leadership and building a movement from a dancing guy. The following key lessons were shared:

- A leader needs the guts to stand alone and look ridiculous, but what he is doing must be so simple it is almost instructional. The key: you must be easy to follow.
- The first follower comes in with a crucial role. He publicly shows everybody else how to follow, and the leader must embrace him as an equal so it is about "them". That follower will call out to his peers to join in and show them how to follow.
- It takes guts to be the first follower. You stand out. **Being a first follower is an underappreciated form of leadership. The first follower transforms the lone nut into a leader.** If the leader is the flint, the first follower is the spark that really makes the fire.
- Once the second follower joins in, it is proof that the first follower has done well. Now it is not a lone nut, or two lone nuts, but as the video states, "three is a crowd and a crowd is news." A movement slowly emerges.
- A movement must be public. Everybody must see the followers because new followers emulate the followers- not the leader.
- As more people jump in to follow, they gain momentum and there is a tipping point. Following is no longer risky. A movement is born. If there are people that were "on the fence" before, there is no reason not to join in now. They won't stand out or be ridiculed, and will be part of the in-crowd.

The key takeaway for executives in the clinical trials industry embracing new initiatives and change is that if you are a version of the shirtless dancing guy all alone, you must remember the importance of nurturing your first few followers as equals, and making everything about the movement- not you. Be public and easy to follow.

The biggest lesson from this video is that leadership is over glorified. Although it starts with a leader, characterized in the video as the shirtless dancing guy, and a leader often gets the credit, it is really the first follower that transforms a lone nut into a leader. There is no movement without the first follower. We are told that we all need to be leaders, but that would be ineffective. The video's lesson is that "**the best way to make a movement is to courageously follow and show others how to follow. When you find a lone nut doing something great, have the guts to be the first person to stand up and join in.**"

THE FUTURE OF THE AVOCA QUALITY CONSORTIUM

Avoca welcomes greater involvement in The Avoca Quality Consortium from existing Member companies as well as new Consortium Members. Avoca is committed to using the Consortium as a catalyst for change within the industry within a short period of time.

Avoca believes some of the most important keys to success in developing industry best-practice standards for proactive quality management include collaboration and senior executive involvement. We will continue to provide the platform for collaboration and engage the executive leadership of our Members to ensure the best-practice standards developed as part of the Consortium are agreed upon by Members and effectively implemented.

In response to inquiries and increasing interest for support in the implementation of best-practice guidelines, tools, and processes, Avoca is offering interactive training workshops and consulting services to help Member companies effectively leverage AQC tools for individual and collaboratively partnered organizational needs. For more information, please contact Danya.Burakoff@theavocagroup.com.

As we approach the second half of 2014, The Avoca Quality Consortium will obtain strategic inputs from Member organizations to build and refine plans for 2015. The Consortium will assess transformational initiatives that provide the opportunity to significantly enhance the ability to deliver quality across the entire value chain for complex, clinical development programs, especially with partnered sourcing business models and ensuring inclusion of perspectives from the investigator and patient vantage points.

UPCOMING CONTENT AND ONGOING CONNECTIONS

Although the Quality Summit is over, our work for the Consortium is always in motion. The Avoca Quality Consortium team is committed to keeping its Members up to date on our activities throughout the year.

Stay tuned for our Monthly Avoca Quality Consortium Newsletter. It features updates on industry news related to quality management.

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If you are interested in sponsoring Avoca's Member meetings or Annual Quality Summit, please contact Danya.Burakoff@TheAvocaGroup.com or 619-994-8677.

UPCOMING WEBINARS

Tuesday September 23rd at 11 am EST
"Risk Identification/Risk Management and Decision Analytics"

Final presentations, referenced articles and agendas from May 6 and May 7 are posted on the Member Portal. Please use your Member credentials to access.

If you don't have your member credentials, please email Caryn.Laermer@TheAvocaGroup.com

OPINION

Engage with research participants about social media

Craig H Lipset


Pfizer

A growing number of participants in clinical trials are sharing information about their health online. It's time that the drug development community starts to examine how this social media use might compromise the integrity of research studies and how it might also offer new opportunities.

Not long ago, the likelihood of clinical trial participants socializing and sharing information was limited to the clinic waiting room. As such, the risk of conversations among patients leading to the unblinding of experimental treatments in research studies was generally viewed as minimal. Over time, this has changed. During the HIV/AIDS crisis of the 1980s and 1990s, activist patient communities with unmet medical needs attempted to navigate blinded clinical trials to gain access to investigational medicines. At that time, social networks were geographically isolated and did not have the technology to enable rapid dissemination of information on a global scale. But today, patients around the world use the internet and social media to find and share health information and use it in their interactions with healthcare providers. This sharing of information has its benefits, but it can also undermine the scientific integrity of medical research.

It is time for the clinical research community to recognize the impact of these conversations on the conduct and interpretation of blinded clinical trials. Patients must be made aware of the potential implications of social media use on the scientific integrity of the study in which they are participating, and researchers must be trained on the risk in maintaining blinding through their own use of online networks. Perhaps most important, clinical trial sponsors must work with regulators to define pathways to monitor social media use by trial participants to understand if conversations on the internet will affect their interpretation of study results.

Looking forward, clinical trial designs may be enhanced by leveraging the insights from research participant conversations on social media. Organizations are already beginning to take advantage of online communities and other social media channels to improve study recruitment and certain aspects of study design. In late 2012, the US Food and Drug Administration (FDA) approved an Investigational New Drug Application with a crowdsourced protocol developed with an online community of patients, physicians and researchers.

What many have failed to appreciate, however, is that the patient who is online before a trial begins will probably continue to use information via the internet during the trial. A 2013 survey by the Pew Internet Project reported 59% of adults in the US search on the web for health information, a rate that continues to trend upward. The rise of the internet has led to the rise of the 'eParticipant', a term used to describe individuals who engage in social media during their participation in a clinical trial.

One format through which information is shared is blogs. During the initial trials of the Novartis drug Gilenya (fingolimod) for multiple sclerosis, one trial participant maintained an active blog documenting and sharing her experience from her initial screening visit in 2007 through drug approval in 2010 and beyond. Her website (fty720.blogspot.com) even referenced the drug's investigational name, FTY720.

Discussion forums, meanwhile, serve as an active area of online interaction among study participants. For example, during the clinical trials for Incivek (telaprevir), a drug from Vertex Pharmaceuticals for hepatitis C, trial participants maintained online discussions at community sites such as MedHelp.org. These conversations extended into robust conversations on potentially sensitive topics, such as suggesting how to identify to which treatment arm of the trial one had been assigned.

Pioneering platforms such as that hosted by PatientsLikeMe enable patients to share health data to support their ability to select treatment options for optimal outcomes. In addition to sharing perceptions of efficacy and safety for approved products, patients can also track and share data for investigational medicines during clinical trials. PatientsLikeMe used data posted by patients with amyotrophic lateral sclerosis who participated in several ongoing clinical trials in an effort to determine whether the investigational products (lithium carbonate, NP001, KNS-760704 and sodium chlorite) may have therapeutic benefit—and this paper was published while the trials were ongoing[1].

Organizations such as the Society for Participatory Medicine, of which I am a founding member, are committed to ensuring the patient is an active participant in health decision making. But with this empowerment come risks, such as the potential for misinformation or inappropriate self-diagnosis and treatment[2]. Unfortunately, there has been little research on the implications of the eParticipant on the scientific integrity of clinical trials[3]. The eParticipants in these various forums are motivated by the desire to support one another as well as by innate curiosity. They may not appreciate how their activities may undermine the scientific integrity of the study by touching on topics such as eligibility (patients sometimes coach one another on how to meet eligibility criteria), blinding (participants share advice on how to determine treatment assignment) and safety (patients sharing safety events may stimulate other patients to perceive the same symptom, affecting data integrity through a false spike in safety reports).

Just as patients conversing among themselves may put the scientific integrity of a blinded clinical trial at risk, researchers who monitor participant conversations on treatment assignment may jeopardize their ability to maintain their own blinding. If a researcher spots an adverse event conversation on social networks, what should she do? Not only is there a lack of FDA guidance specific to social media in the research setting, but also research sponsors in these situations may struggle to confirm that the patient is truly in the trial and may face difficulty in determining whether the online report is one already captured in the study database. In most cases it is unrealistic to match a posting in a web forum to a randomized patient in a study to confirm the finding.

It is likely that in the near future participants may be counseled by the study investigator at the time of informed consent on limiting social media use during their involvement with a clinical trial, or that research investigators and sponsors themselves may receive training to ensure that their blind is maintained. As one trial participant counseled me—"we are human beings and we will talk; patients are not going to change, so the researchers must." As use of online networks continues to rise, research sponsors and regulators must begin studying the implications of social media on the integrity of current blinded and randomized clinical trials.

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Quality by Design in Clinical Trials: A Collaborative Pilot With FDA

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Abstract

The quality of a clinical trial can be assessed by whether the trial meets the needs of its various customers, as well as by its freedom from critical deficiencies or errors. In order to ensure the quality of a clinical trial, it is therefore important to conduct quality planning in parallel with the process to design and prior to the conduct of the trial. Quality planning consists of prospectively establishing quality goals and developing the products and processes required to deliver a quality trial. This article describes the quality planning process conducted by a pharmaceutical sponsor for a clinical trial and the pilot review of the resulting integrated quality management plan by the FDA. This pilot demonstrates the usefulness of this process to enable alignment between sponsors and regulators concerning quality in clinical trials.

Keywords

clinical trials, quality planning, quality by design, FDA, integrated quality management plan.

Introduction

Over the past several years, a number of articles have characterized and promoted various approaches to quality assurance for clinical trials.[1-6] Much of this literature has focused on the monitoring process or source document verification and on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice E6, which provides guidance on the monitoring of clinical trials.[7] To our knowledge, there has been a paucity of articles discussing an overall quality framework or Quality by Design (QbD) principles applied to clinical research or clinical trials. Recently, both the US Food and Drug Administration (FDA) and European Medicines Agency have published draft guidance documents that make recommendations regarding risk-based monitoring and quality risk management in clinical trials.[8,9]

Juran is often credited with introducing the concepts underlying QbD. The Juran Trilogy consists of three activities: quality planning, quality control, and quality improvement.[10] "Quality planning is the activity of (a) establishing quality goals and (b) developing the products and processes required to meet those goals."[10] Specific methodology, skills, and tools have been developed to enable quality planning. Quality control is the process of evaluating actual performance against quality goals and taking corrective action where necessary. Quality improvement is "the means of raising quality performance to unprecedented levels."[10]

The Clinical Trials Transformation Initiative (CTTI; http://www.ctti-clinicaltrials.org/) is a public-private partnership between the FDA and Duke University, with a diverse membership from academia, clinical research organizations (CROs), biopharmaceutical and device companies, patient and consumer representatives, professional societies, government researchers, and other government agencies whose mission is to identify practices that through broad adoption will increase the quality and efficiency of clinical trials. In response to CTTI's efforts to characterize and improve the efficiency and effectiveness of monitoring,[11] we undertook a pilot applying QbD tools and methodologies to a clinical trial for a novel potential therapeutic for the treatment of a neurological disease. Consistent with the approach taken in developing QbD

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Aspects of this work were presented at the DIA 2011 47th Annual Meeting on June 19-23, 2011 in Chicago, Illinois.

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approaches for drug products,[12] Pfizer sought FDA review and feedback on both the QbD approach and the specific parameters defined for the clinical trial. This manuscript specifically summarizes the quality planning methodology and output and does not discuss the quality control or quality improvement aspects of the Juran Trilogy.

Methodology

Pfizer and FDA's Division of Neurology Products (DNP), Center for Drug Evaluation and Research (CDER), and Office of Scientific Investigations (OSI), Office of Compliance agreed to undertake a pilot to test one model for prospectively designing quality into clinical trials. The pilot involved a development program scheduled to start pivotal studies. A first submission of the outline of a pilot Integrated Quality Management Plan (IQMP) was made to the FDA in September 2010. This was followed by a combined meeting between Pfizer and both the DNP and OSI in November 2010. Following on further refinement of the initial proposal, feedback from the FDA, and completion of the IQMP planning process, Pfizer submitted a second iteration in March 2011. FDA provided feedback on this second submission to Pfizer in June 2011.

The quality planning methods applied by Pfizer in the pilot with FDA were collectively described in the IQMP. The IQMP-based approach to quality was founded on three main principles:

1. Quality is built in at the time of protocol development and systematically managed during study conduct through a process of continuous improvement.
2. Quality goals and relevant quality metrics are prospectively identified and measured throughout the duration of the study.
3. Risks to quality are prospectively identified, prioritized, and mitigated.

Continuous Improvement

The Plan-Do-Check-Act (PDCA) methodology, as illustrated in Figure 1, is the framework upon which the system of continuous improvement is based.[13] This article will cover the "Plan" phase of the PDCA cycle, which constitutes the quality planning activities.

The following describes, in the context of a quality management system for clinical trials, the activities/actions that are associated with each phase of this process.

Plan

- Prospectively identify the objectives that are critical to quality that must be met during the conduct of the clinical trials in order to meet stakeholder needs (ie, where quality matters most).

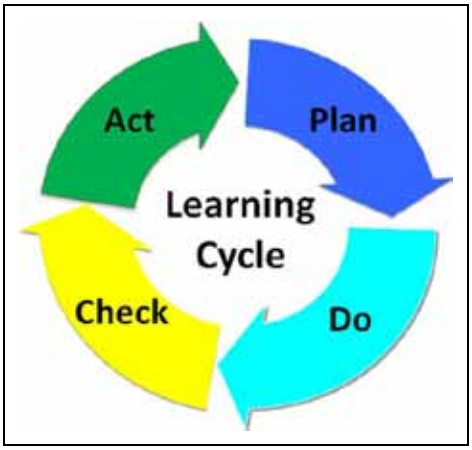

Figure 1. Plan-Do-Check-Act (PDCA) methodology. The continuous learning cycle of planning, executing, measuring, and then responding to measurement deviations.

- Define metrics that will enable real-time measurement of quality performance in relation to the predefined quality objectives.
- Systematically examine the development candidate, the planned clinical trial, and the clinical operations process in order to prospectively identify and prioritize risks to quality.

Do

- Implement quality risk management plans during the conduct of the clinical trials.

Check

- Measure/monitor quality performance, on the basis of the metrics previously identified, to assess whether quality objectives are being met and to enable identification of unanticipated risks.

Act

- Respond to quality issues with appropriate corrective and/or preventive actions.

Quality Objectives

The following are generally recognized as the common objectives of quality management in clinical trials:

- patient safety and rights,
- data quality and trial integrity,
- compliance with the investigational plan.

Pfizer identified critical-to-quality (CTQ) requirements for the clinical trials based on these common objectives. For example, whether or not all subjects randomized meet inclusion/exclusion criteria set out in the investigational plan may impact

data quality and study integrity (ie, was the intended population enrolled) and subject safety (ie, were subjects enrolled for whom participation may not be advised). For each CTQ, one or more metrics were identified to facilitate the measurement and monitoring of quality performance during the conduct of the clinical trials. For each metric, target (nominal) values and upper or lower specification limits (action thresholds) were determined. A metric crossing the action threshold would require Pfizer to conduct an investigation, which might include a root cause analysis to address the issue. Examples of CTQs and their associated metrics are given in Table 1.

Prospective Risk Assessment

To build quality into the clinical trials, it is necessary to systematically examine the study drug, the clinical trial design, and the clinical operations process to prospectively identify and prioritize risks to quality. The high-level clinical trial process reflected in Figure 2 was used as a framework to facilitate risk assessment of the trial design and clinical operations.

This risk assessment and prioritization process involved:

- Identification of protocol-specific risks associated with each operational process area or related to critical aspects of the clinical trial design;
- Prioritization of risks based on their severity, frequency of occurrence, and the ability to detect occurrence. Risks were prioritized based on the product of the scores for severity, occurrence, and detection. Table 2 describes the scales and corresponding definitions used to guide the risk prioritization process;
- Development of risk management plans to reduce the occurrence of the potential cause and/or improve detection if the risk were to occur, for potential high priority risks.

CDER Integrated Quality Management Plan Review

OSI reviewers began with an evaluation of the study design and protocols to determine which data and processes might be critical to evaluating trial results and to protecting participants. For example, a critical clinical trial process might be a clinical assessment generating primary endpoint data. OSI reviewers considered risks to the successful conduct of these processes and collection of these data. For example, significant inconsistency across clinical sites in carrying out an assessment for the primary endpoint might impede analysis. Finally, the reviewers determined what aspects of the protocol design might prevent or mitigate critical risks. For example, the protocol could require specific training for those carrying out the primary endpoint assessment or describe planned, ongoing review of primary endpoint data to identify unexpected variability within or across sites to permit follow-up and retraining of investigators, as necessary.

With this upfront understanding, OSI reviewers then considered (1) what the sponsor considered to be critical to quality data and processes, (2) how the sponsor prospectively identified risks, and (3) how the sponsor planned to manage important and likely risks to the trial. Feedback provided to the sponsor centered on ensuring that all important risks to trial integrity and subject safety were appropriately managed. For example, OSI recommended that the sponsor consider additional measures to ensure the timeliness of a vendor's completing and reporting the results of an analysis important to determining subject eligibility and to ongoing safety monitoring. OSI staff closely evaluated the sponsor's risk prioritization, recommending that the sponsor consider whether efforts devoted to lower risk activities with minimal impact on subject safety and/or data integrity might be reduced or eliminated. In particular, OSI sought to identify areas for greater alignment between planned oversight activities and the requirements of FDA regulations or recommendations in guidance. OSI also provided feedback on processes, such as audits, in place to identify risks unanticipated at the time of IQMP development. Finally, OSI evaluated whether the planned critical to quality measures were reasonably likely to ensure effective, ongoing monitoring of risks to study quality.

Discussion

Pfizer Perspective

The Pfizer team that participated in the IQMP pilot included individuals from all relevant clinical trial execution functions, including clinical, statistics, clinical pharmacology, quality assurance, clinical safety, clinical project management, study management, data management, pharmaceutical sciences, and regulatory.

The process enabled an integrated, cross-functional approach to building quality into the clinical trials. This was, in some cases, the first time the team had considered an integrated approach to mitigation of risks to quality across functional lines. As a consequence, the team collectively developed a wider appreciation for factors that were critical to quality, what risks were most likely to impact quality during study conduct and reporting, what could be done to mitigate these risks, and how quality issues in one functional area could result in quality risks in another. For example, when the study team considered the risks related to the study Drug Administration Instructions (DAI), the risk that instructions might be misunderstood or incorrectly implemented were identified. Mitigation of these risks required a collaboration between pharmaceutical sciences, study management, data management,

Table 1. Listing of critical-to-quality (CTQ) factors and measures.

CTQ Factor	CTQ Measure
SAEs and other reportable information are reported from site to sponsor in a timely manner	Percentage of SAEs and other reportable information reported from site to sponsor within 24 hours of investigator awareness
Trials are overseen to monitor existing and/or identify new/emerging safety signals	Safety review frequency as per SOP
Investigators (principal and subinvestigators) are appropriately trained prior to performing any subject-related activities	Percentage of investigators (principal and subinvestigators) trained on study-specific requirements for each study
	Percentage of principal investigators trained on study-specific requirements for each study prior to performing any subject-related activities
CRAs/monitors are trained prior to performing any study related activities	Percentage of CRAs/monitors trained on study-specific requirements for each study to which they are assigned
Investigational product, comparator(s), and placebo(s) as appropriate are received, stored, prepared, handled, and dispensed at the site according to the appropriate study procedures	Percentage of dosings of investigational product, comparator(s), or placebo(s) as appropriate that are inappropriate due to improper site receipt, storage, preparation, handling, or dosing
Each participating investigator is provided information necessary to conduct the investigation properly and is informed of new observations on the investigational product, particularly with respect to adverse effects and safe use	Investigators are notified promptly using protocol deviation alert letters for new observations related to adverse effects and/or safe use of the study drug as appropriate, with no investigators having been missed
All subjects randomized meet inclusion/exclusion criteria	Percentage of subjects randomized that do not meet inclusion/exclusion criteria at the time of randomization
All study procedures are completed as per the protocol	Percentage of subject visits at which protocol deviations related to improper study procedures are identified
Study subjects do not take prohibited concomitant medications or vaccinations	Percentage of subject visits at which protocol deviations due to prohibited concomitant medication or vaccinations are identified
All subjects are properly consented prior to study enrollment and/or properly reconsented during study conduct (if required)	Percentage of subjects with inadequate informed consent
CTA and/or IRB/Ethics Committees approval is obtained from countries and sites before enrollment begins in those countries or sites	Percentage of investigational product shipments without approved Investigator Initiation Package or equivalent in place
Data are reviewed promptly for early identification of potential quality or subject safety or data protection compliance issues	Percentage of subject data reviewed within 15 calendar days
Data are entered by the site into the database in a timely manner and the database is accurate and complete	Percentage of subject visits meeting data entry target timelines within 4 calendar days
	Percentage of study sites with no data outstanding greater than 30 calendar days
	Percentage of unresolved queries in the database for longer than 30 calendar days
Vendor data are received and loaded into the database in a timely manner and the database is accurate and complete	Percentage of defined patient data not received from vendor for current transfer cycle
	Percentage of vendor data queries remaining unresolved at next data transfer
Investigational product, comparator(s), and placebo(s) as appropriate are manufactured, packaged, stored, and shipped to the site according to cGMP	Number of critical GMP incidents related to improper manufacturing, packaging, storing, or shipping of investigational product leading to a customer complaint
	Number of major GMP incidents related to improper manufacturing, packaging, storing, or shipping of investigational product leading to a customer complaint
	Number of minor GMP incidents related to improper manufacturing, packaging, storing, or shipping of investigational product leading to a customer complaint
Adequate investigational product, comparator(s), and placebo(s) as appropriate are available at all sites	Number of subjects that cannot be dosed due to lack of investigational product, comparator(s), or placebo(s) as appropriate
Study-level subcontracted services are routinely assessed and documented to ensure quality oversight and performance	Percentage of planned subcontractor quality and performance review meetings that occurred as planned and are documented
The TMF is accurate and complete in accordance with the study-specific document list	Percentage TMF completeness
	Percentage TMF on-time submissions

SAE, serious adverse event; SOP, standard operating procedure; CRA, clinical research associate; CTA, clinical trial authorization; IRB, institutional review board; GMP, good manufacturing practice; cGMP, current good manufacturing practices; TMF, trial master file.

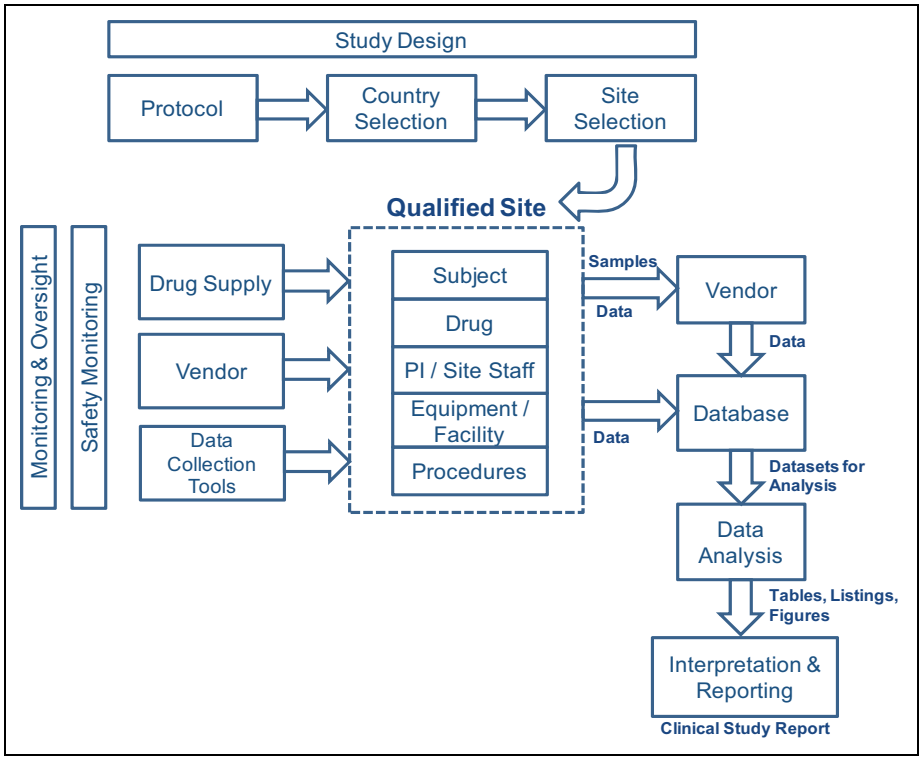

Figure 2. High-level clinical trial process: the process steps that apply to most clinical trials. Used as a framework for assessing risks in clinical trial design and clinical operations.

Table 2. Risk level definitions.

Risk Level	Definitions		
	Severity	Occurrence	Detection
1	Minor impact to data quality/study integrity *or* compliance with the investigational plan	Likelihood of occurrence is remote (rare or never)	Most likely to be detected immediately
4	Minor impact to patient safety/rights, *or* significant impact to data quality/study integrity, *or* compliance with the investigational plan	May occur occasionally (sometimes)	Most likely to be detected at a quality control check point
7	Significant impact to patient safety/rights, *or* major impact to data quality/study integrity, *or* compliance with the investigational plan	May occur frequently (most of the time)	Most likely to be detected by an internal audit
10	Major impact to patient safety/rights (eg, life threatening) *or* major impact to both data quality/study integrity *and* compliance with the investigational plan	Certain to occur (all the time)	Most likely to be detected by a third-party external audit or inspection

and clinical. This collaboration resulted in the rewriting of the DAI document from a QbD perspective, resulting in more clarity in the written description of the process and instructions regarding study drug administration. Before deployment, the team tested the clarity and comprehension of the revised document with site pharmacists. The cross-functional approach to quality provided more formal opportunities for the team to systematically discuss, assess, and measure quality. The heightened awareness of risks allowed the team to take greater ownership of quality in the clinical trial.

CDER Perspective

Traditionally, sponsors have relied on intensive on-site monitoring and audit programs focused on clinical investigators to ensure the quality of their clinical trials. FDA and its stakeholders share a concern that this model may be unsustainable in a global, complex clinical trial environment.

Existing practices are generally reactive and resource intensive, not risk adapted. Moreover, they may be poorly suited to preventing or mitigating all critical risks, in particular the risk of systemic error introduced during trial design and planning.

Modernizing clinical trial oversight is a key initiative of the FDA. Approaches, such as that undertaken in the present pilot, that build quality into clinical trial design and incorporate principles of risk management may enhance the quality and efficiency of clinical trials. Such approaches facilitate sponsors in identifying and analyzing risks to trial quality and subject safety and in focusing their resources on addressing the most significant risks. Importantly, they also free sponsors from the perceived need to mitigate every risk, particularly those risks that would be expected to have no or minimal impact on data integrity and subject safety.

Conclusions

This IQMP pilot lays a promising foundation for overseeing clinical trials and provides one example of a range of feasible approaches to adopting QbD and risk-based oversight in clinical trial execution. FDA and Pfizer plan to continue piloting this process into the Do-Check-Act cycle. We anticipate that we will continue to gather important data and lessons learned through this real-time testing that will permit Pfizer to further refine the IQMP model and FDA to continue to evaluate the feasibility, including the processes and resource requirements, of undertaking routine review of such prospective submissions. We believe that engaging in prospective dialogue about quality risk management in trials can enhance quality without unduly stifling study conduct.

Declaration of Conflicting Interests

Kenneth Sprenger and David Nickerson are employees of Pfizer Inc. Ann Meeker-O'Connell and Briggs W. Morrison were previously employed by Pfizer Inc, with no current financial arrangement with Pfizer.

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How to Fix the Protocol Complexity Problem

Publish date: Feb 27, 2014
By: Lisa Henderson

Would you delay protocol approval by two months if it meant your enrollment and retention would improve and, in turn, positively affect your data quality?

With all the data and downstream impact of a overly complex or poorly designed protocols in hand, it appears that this phenomenon is taking hold, but hasn't hit mainstream yet. At CBI's Clinical Trial Budgeting and Project Management conference earlier this week, sponsors shared both their successes and challenges in reigning in protocol creep.

There is no doubt that everything about protocol design has come under the microscope in the past couple of years. And it came to a head when Tufts CSDD announced its analysis of the costs surrounding protocol amendments and non-core protocol procedures. The Tufts analysis was based on data from Medidata Solutions' PICAS database of industry-wide negotiated site cost information. Survey analyst Ken Getz noted that the key takeaway is "that study performance and efficiency are highly associated with protocol feasibility. Any and all attempts to simplify protocol design and reduce complexity will reduce cost, shorten cycle time, and improve patient recruitment and retention effectiveness."

What this analysis did not directly quantify was the downstream effects of protocol complexity on recruitment and retention. Medidata itself delved into its Insights database to answer that question in this article, however, it did say the metrics used were from different areas of its data warehouse. So it found that there is an increase in protocol complexity and is accompanied by a downward trend in the ratio of enrolled-to-screened patients. However, "there is not a one-to-one direct relationship or correlation between protocol complexity in a study and enrollment rates in that same study, at a macro level, this analysis highlights that increasing complexity of protocols correlates with either higher patient screening or lower patient enrollment, or both."

It is more than anecdotally correct that putting a patient first in the protocol design, as is heard at patient engagement conferences or in regard to patient-centric trial design, will increase both recruitment and retention rates.

Merck recently revamped its processes around site start-up—from site contracts to site readiness to how it works with its outsourcers—and reported increases in efficiencies at the conference. These changes started incrementally in 2012 throughout further implementation in 2013, which shows positive outcomes. However, next year should provide more in-depth data.

Merck's new protocol development process involves an Investigator Scientific Network that includes investigators who are also clinicians. Their input is usually centered on the different points related to standard of care and potentially point out that a procedure would not be necessary in a real-world setting. In addition to this network, Merck has instituted a process of three internal pre-reviews before protocol approval to apply the scientific rigor to a cost process.

Sponsor speakers at the conference noted it really is important to ask the medical officer or scientific lead if that one extra blood draw is necessary during the protocol development stage, and push back if the view is that it is not. Even a lead investigator or outside KOL with experience in the therapeutic area can offer real-world input into a protocol that can also help cut costs.

In site feasibility, it is crucial to go over the protocol from a patient's journey. In one study described by a speaker from AstraZeneca, it was determined that enrolling in a stroke study in a hospital that potential patients were being missed. In an analysis of the emergency room procedures, it turned out that all stroke patients received oxygen from a nurse prior to the physician. The respiratory nurse was then educated on the protocol and asked to contact the clinical study nurse for potential screening. After that, the patients were no longer missed.

Transparency Life Sciences, which uses an online crowdsourcing protocol builder, was brought up by the speakers as an interesting approach for designing and streamlining protocols. The company most recently partnered with Icahn School of Medicine at Mount Sinai to design and conduct a trial assessing metformin as a treatment for prostate cancer. That trial will use crowdsourcing to obtain input into the design of the protocol, which will assess the use of telemonitoring to replace most patient visits.

Scrutinizing Non-Core Protocol Procedures

Publish date: Mar 1, 2013
By: Kenneth A. Getz

The period from 2010 to 2020 may well come to be recognized as the decade of protocol design optimization. Having spent the past 20 years implementing strategies and tactics that have had a marginal-at-best impact on reducing study cycle time and costs, sponsors and CROs are now looking in earnest at protocol design optimization as the key to driving fundamental and sustainable operating efficiency and speed.

Initiatives to optimize design and improve protocol feasibility include modifying authoring templates and inviting input from investigative sites and patients. Recent research from Tufts CSDD assists sponsors and CROs in targeting their focus on those procedures that are less essential to the objectives of the protocol and determining whether it is critical to perform them.

Protocol scope creep

Results of the 2012 study suggest that sponsors are spending more than $5 billion annually in direct costs to administer protocol procedures that are not tied to primary or key secondary endpoints and regulatory requirements. The incidence of these less essential or "non-core" procedures has nearly doubled during the past decade.

Non-core procedures are added to protocols for a variety of reasons: Clinical scientists and statisticians, for example, may want to collect more contextual data to help interpret study findings and guide development decisions. Context-setting variables may not appear in any statistical plan but they may provide clinical validation and explanation for unusual and unexpected results that may be observed during a clinical trial. Clinical scientists also collect additional study data hoping that, should the study fail to meet its original objectives, post-hoc analyses might reveal useful new insights into the characteristics and treatment of disease.

The presence of non-core protocol procedures may also be a function of authoring processes and practices and as an insurance policy against risk. Medical and protocol writing professionals may permit outdated and unnecessary procedures into new protocols because they are routinely included in legacy authoring templates and policies. Clinical teams collect additional data in cautious anticipation of requests for data from regulatory agencies, purchasers, and payers.

Study methods

Medidata Solutions sponsored the research study and 15 mid-sized and large pharmaceutical and biotechnology companies participated. Each company provided data on approximately 10 Phase II and III protocols targeting diseases across multiple therapeutic areas and executed by investigative sites dispersed globally since 2009. To minimize unusual and atypical designs, pediatric, medical device, orphan drug, and extension studies were excluded from the sampling frame. In all, 116 unique Phase II and III protocols having at least one procedure tied to a primary endpoint were analyzed. Participating companies classified each protocol procedure according to the objective and endpoint it supported as defined by the clinical study report (CSR) and the study's specific statistical analysis plan (SAP). In total, 25,103 procedures were classified along the following lines:

"Core" procedures. Those that support primary and/or secondary study objectives, or primary or key secondary and safety endpoints.

"Required" procedures. Those that support screening requirements and compliance-related activity including drug dispensing, informed consent form review, and study drug return.

"Standard" procedures. Those that are commonly performed during initial and routine study participant visits including medical history, height and weight measurement, adverse event assessment, and concomitant medication review.

"Non-Core" procedures. Those that support supplemental secondary, tertiary and exploratory endpoints, and safety and efficacy procedures not associated with a study endpoint or objective.

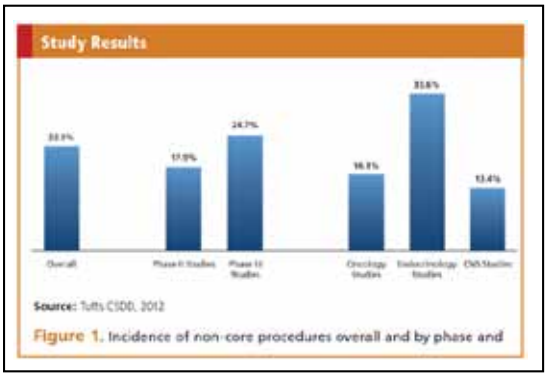

Figure 1. Incidence of non-core procedures overall and by phase

The direct cost to implement each protocol procedure was also analyzed using Medidata Solutions PICAS® database. Direct cost data for 16,607 procedures was analyzed.

Incidence and direct cost

Characteristics of the protocols analyzed in this study—i.e., number of countries, sites and patients; total number of procedures and eligibility criteria—were consistent with industry benchmarks. Overall, half of the total procedures per protocol were classified as "Core" to the study. These procedures supported primary or key secondary endpoints. More than one out of every five procedures (22.3%) overall were "Non-Core" as they supported supplemental secondary, tertiary, and exploratory endpoints. One out of every four (24.7%) procedures performed per Phase III protocol and 17.9% of all Phase II procedures were classified as "Non-Core." "Core" procedures made up approximately half of all procedures by phase—47.9% of Phase III and 54.3% of Phase II studies. Variability across therapeutic areas was observed with endocrine protocols having the highest incidence of non-core procedures.

The distribution of direct costs was similar to that of procedure count. Overall, an average of $2.9 million of the total direct procedure costs per study—47.9%—was spent to administer "Core" procedures. An average of $1.1 million per protocol (17.9%) was spent to cover the direct cost of performing "Non-Core" procedures. The direct cost to administer "Required" and "Standard" procedures for Phase II and III protocols cost an average of $1.3 million (21.7%) and $.8 million (12.5%) respectively.

For Phase III protocols, the average total direct cost to administer all procedures was $9.4 million. Approximately half of the total direct cost (46.0% or $4.3 million on average) was spent to administer "Core" procedures; 18.5% or $1.7 million on average was spent to administer "Non-Core" procedures. The direct cost to administer procedures supporting screening requirements and regulatory compliance were $2.2 million or 24% of the total. "Non-Core" procedure administration costs were on average $.3 million or 13.1% of the total direct costs for Phase II protocols.

Discussion

Sponsors and CROs have long noted the expansive and increasing scope of their study designs and the rapid growth in the amount of data collected and analyzed per protocol. This recent Tufts CSDD study, however, provides hard metrics quantifying the incidence and direct cost of non-core procedures—a major source of expanding protocol scope. The marginal cost of including a single non-core procedure may be very small relative to the overall total study budget. But in the aggregate, non-core procedures consume 20% of the entire study budget.

Given that an estimated 2,578 Phase II programs and 1,079 Phase III programs were active worldwide last year, the total direct cost of collecting data from non-core procedures supporting these programs in 2012 was an estimated $4 billion. This is a very conservative estimate as it only counts an investigational drug in clinical development once, despite the fact that many drugs are in active clinical trials for multiple indications. The estimate also only counts one clinical trial per active compound per phase, when multiple trials are often conducted simultaneously.

These direct cost estimates also do not include any of the costs associated with having personnel capture, monitor, clean, analyze, manage, and store tertiary and exploratory procedure data. Indirect costs may be four to six times higher than the direct costs. The Tufts CSDD study also did not attempt to estimate the ethical costs of exposing study volunteers to unnecessary risks associated with conducting non-core procedures.

The primary takeaway of this study is not that clinical trials are a waste of resources as was suggested by a journalist reporting on a presentation of the results that I gave several months ago. The key message is that study performance and efficiency are highly associated with protocol feasibility. Any and all attempts to simplify protocol design and reduce complexity will reduce cost, shorten cycle time, and improve patient recruitment and retention effectiveness.

Non-core procedures are the place to begin. These procedures should be more carefully scrutinized and the trade-off between their benefits and cost assessed. As part of that assessment, sponsors and CROs can determine whether to delay or remove non-core procedures if the cost of doing so outweighs their benefit.

The recent Tufts CSDD study provides a framework for sponsors and CROs to identify and challenge non-core procedures. This framework may prove invaluable in helping sponsors prioritize and redirect scarce resources and capital. As we enter the decade of protocol design optimization, more prudent and active evaluation of non-core procedures is an unusual win-win opportunity for sponsors and CROs to dramatically improve performance and efficiency while lowering costs.

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–Pancreatic cancer trial participant

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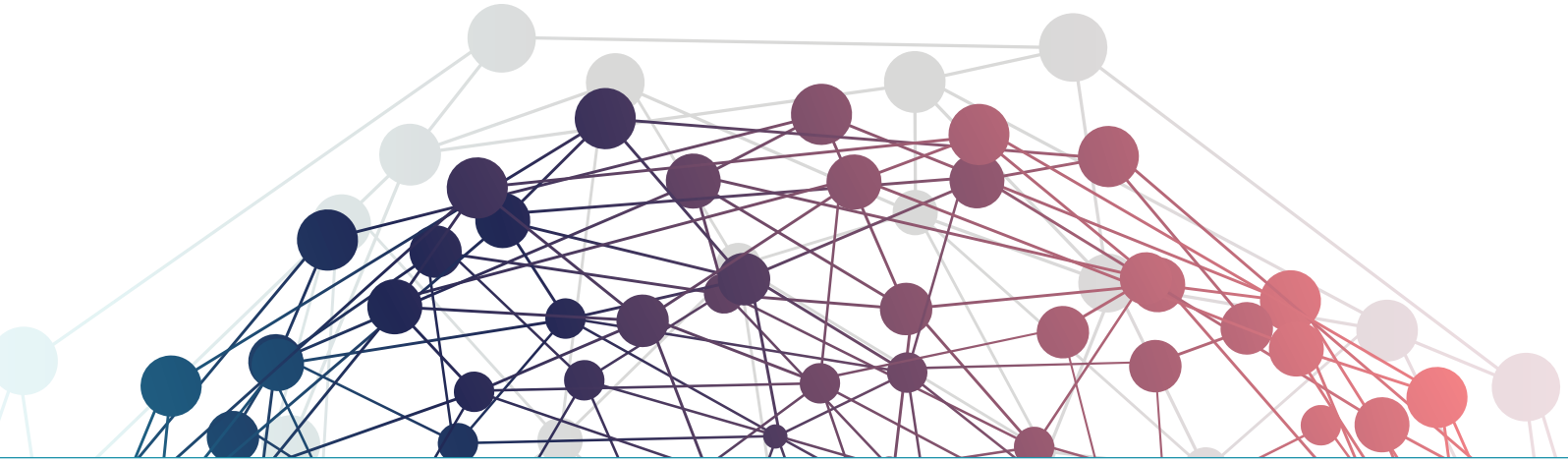

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