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Applied Clinical Trials

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Blockchain in Research, from Business to Personal

LISA HENDERSON
Editor-in-Chief

Applied Clinical Trials has featured articles and discussion around the concept of blockchain (bit.ly/2ANQtpD and bit.ly/2SNPLzh). But it's becoming a bit clearer that blockchain is moving toward definitive uses quickly in the clinical trials world.

At the recent CBI Interactive Response Technologies (IRT) 2018 conference, Imran Shakur, senior manager, clinical supply capabilities for Biogen, and Chad Sklodosky, director, digital clinical supply chain at Pfizer, presented on the topic "Leverage Blockchain Technology to Enhance Supply Chain Management." Sklodosky described a November 2017 blockchain workshop held at Pfizer's Research Technology Center in Cambridge, where over 50 participants from various companies discussed 12 use cases, of which two working groups were advanced.

The one discussed at this conference was the Clinical Supply Blockchain Working Group, whose long-term vision is to "develop a fully interoperable, transparent, and auditable platform that enables investigational product (IP) to be tracked from point of manufacture to the point of which it is consumed by the patient." Sklodosky outlined the working group's timeline around clinical supply, with the 2023 goal of having fine-tuned a process that will be scalable to the ecosystem.

The second use case that the group decided to advance was patient data donation and clinical research, which was not presented at this conference, but more can be learned from a recent paper issued by Deloitte and Pfizer (see bit.ly/2OnmVm8).

In this outline, the patient becomes the owner of their data and chooses where that data is stored and shared in the trusted blockchain network. As the paper points out, the patient could seek out clinical research opportunities or donate their data to research efforts. While CISCRP has conducted many studies on the altruistic reasons people participate in clinical trials—to help others benefit—this data donation would surely take that step one further.

Hu-manity.co agrees that data ownership is fundamental, however, it also believes individuals should be paid for their data. I refer to this news blurb, bit.ly/2DnpiEo, and this longer article about one of the co-founders, bit.ly/2zqlD4i. Hu-manity.co is partnering with IBM to use its blockchain platform as its global consent ledger, whereby people will manage consent, authorization, and commercial use of their personal information. This information is not limited to medical, health, or research data, but is definitely a part of co-founder and COO Michael DePalma's larger position, as quoted in the referenced article. He also says in the article "there is a massive amount of valuable data being generated, but none of the profits are being filtered back to the people who create the value."

In the business case use above, data ownership is not the question. Those that consent into the private clinical supply chain process participate around the data flow. Interestingly, during Sklodosky's presentation he said that blockchain in this case could appear to be doing away with IRT. However, he explained that IRT is actually blockchain "lite" and experts in IRT are needed to guide the forward solution.

While the way data is collected and stored in this industry evolves from legacy to cloud-based systems; integration issues and actionable insights around data, it's the data itself that is moving into the center stage.

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FEATURED

WASHINGTON REPORT

FDA INITIATIVES ADVANCE ORPHAN THERAPIES

Streamlined clinical trials and continued patient involvement in product research continue to advance the development and market approval of more innovative therapies for rare conditions. FDA has approved more than 60 orphan indications for new and existing products this year, building on 80 approvals for 2017, according to a study from the IQVIA Institute for the National Organization for Rare Disorders (NORD) (see bit.ly/2SumlWR). FDA approvals of new treatments are "shattering previous records" based on continued innovation in research in this area, observed NORD President Peter Saltonstall in conjunction with NORD's annual Rare Disease Summit in Washington, D.C. in October.

Important FDA initiatives aim to increase the use of biomarkers and provide early advice to sponsors to make clinical trials more efficient and less costly for developing targeted therapies, including those for rare conditions. An important draft guidance issued in October encourages sponsors to use "minimal residual disease" (MRD) as a biomarker in testing drugs or biologics to treat certain blood cancers (bit.ly/2CQXx63). This general measure of tumor burden in clinical trials, observed FDA Commissioner Scott Gottlieb in announcing the advisory, has the potential to expedite product development by assessing a patient's response to treatment or the risk of future relapse. The policy supports using MRD to enrich clinical trial populations and define treatment arms, with an eye to further developing the marker as a surrogate endpoint.

The agency also finalized a guidance on identifying treatments that address underlying factors that may contribute to disease, such as rare molecular changes present in small subsets of patients (bit.ly/2Jrv4Fc). This advisory aims to help sponsors enroll in clinical trials those patients with genetic markers that indicate likely response by providing information on grouping patients with different molecular alterations and on strategies for evaluating the benefits and risks of targeted therapies to treat diseases with rare molecular alterations.

More support

Sponsors, researchers, and patients can obtain advice and information through a new FDA web portal on "developing products for rare diseases," which aims to provide a "central home" on FDA regulatory initiatives and programs in this area (bit.ly/2PyFUyE). A guidance published earlier this year, moreover, clarifies FDA's orphan drug designation process, which opens the door for sponsors to gain expedited reviews and financial support for clinical studies and other processes (bit.ly/2AA6aAl). To help shape early R&D programs for therapies for rare diseases, FDA is encouraging sponsors to sign up for pre-investigational new drug (IND) meetings to discuss studies that utilize smaller patient pools. Another FDA guidance spells out what manufacturing and preclinical data is needed to make such early meetings useful, and what expedited programs, standards, and support is available to researchers seeking to test new treatments (bit.ly/2yF9UPB).

A broader agency reorganization plan announced by Gottlieb in July aims to better coordinate advice and oversight for orphan drugs by establishing an Office of Clinical Policy and Programs (OCPP) that supports cross-cutting clinical programs involving multiple FDA medical product centers. Under the new structure, OCPP will report to FDA Deputy Commissioner Rachel Sherman and include the Office of Orphan Products Development (OOPD), the Office of Pediatric Therapeutics, the Office of Combination Products, and a new Office of Clinical Policy. OCPP also will oversee an expanded agency-wide program for patient affairs and healthcare providers to enhance engagement with these external stakeholders.

FDA officials plan to expand OOPD's staff and programs under Janet Maynard, newly named acting director of the office. And FDA's new orphan product council is meeting regularly and assisting in the development of additional guidance documents, reported Sherman at the NORD summit.

These initiatives stop short of establishing a separate FDA center of excellence for rare diseases, as sought by patient advocates in this area. But the planned organizational changes will mean that the oversight of new therapies for rare diseases, said Sherman, "will never become orphans" at FDA.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

10/24/18: Testicular Toxicity: Evaluation During Drug Development Guidance for Industry

10/15/18: Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings Guidance for Industry (draft)

10/15/18: Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease; Guidance for Industry (draft)

10/15/18: Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry (draft)

10/11/18: Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations

9/28/18: Adaptive Design Clinical Trials for Drugs and Biologics (draft)

EU REPORT

EUROPE MULLS RIVAL APPROACHES TO TACKLING DISEASE

October offered a striking spectacle of contrasts in Europe's ponderous attempts to construct a comprehensive policy on health.

On the one hand, the month opened with calls from a cross-party group of members of European Parliament (MEPs) seeking action from the European Commission in support of orphan drugs and rare-disease patients. "What measures has the Commission taken so far to ensure accurate and timely diagnosis of rare diseases," ask the MEPs. In addition, they pointed out, patient access to medicines for rare diseases varies widely across Europe—so what is the Commission doing to promote the availability of affordable medicines to treat rare diseases, they demanded.

Throughout the month, groups as diverse as the European Alliance for Personalized Medicine and the Multistakeholder Paediatric Strategy Forum have been urging vigorous action to promote targeted treatments, close collaboration on dialogue between regulators and drug developers, and early scientific advice—with much of the discussion centered on the emerging plan for coordinated European-level health technology assessment (HTA).

Conversely, the month was also marked by a crescendo of concern that health policymakers may be looking through the wrong end of the telescope with their traditional focus on treatment. Right at the start of October, one of Europe's biggest annual health policy gatherings, the Gastein forum, named for the mountain resort in Austria where it takes place, heard plenty of calls for a bigger and better European health policy—but with an emphasis on wider access and greater equality, and with a focus on prevention rather than treatment.

A series of prominent healthcare policymakers, from World Health Organization (WHO) Regional Director for Europe Zsuzsanna Jakab, to Director of the European Center for Disease Prevention and Control Andrea Ammon, underlined what they saw as the need for a multisectoral, societal, and integrated response to health. There were repeated invocations of the United Nations' Sustainable Development Goals (SDGs), and calls for Europe to lead by example in the program's global ambitions to tackle poverty, inequality, climate, environmental degradation, and injustice.

EU's Commissioner for Health Vytenis Andriukaitis has taken as his theme "the importance of our health-in-all-policies approach." He told a WHO meeting in Kazakhstan: "We need a much stronger focus on health promotion, protection, and disease prevention." And Andriukaitis has developed the theme throughout the month, with speeches endorsing the merits of a broader approach. The mantra is that the health sector cannot succeed alone. "We must address all the risk factors in a more holistic way: obesity and unhealthy nutrition, lack of exercise, tobacco, alcohol abuse, and also wider factors such as working conditions, unhealthy housing, and environment pollution" he said.

Andriukaitis followed a similar line at the G20 Health Ministerial Meeting in Argentina where childhood nutrition was on the agenda, and at the recent UN high-level meetings on non-communicable diseases and tuberculosis.

It is more than just a straw in the wind that the EU has set up a new steering group on health promotion and prevention of non-communicable diseases that is tasked with identifying priority areas for action and promoting exchanges of policies and practices between countries. Nor is it entirely a coincidence that it has chosen nutrition and physical activity as one of the areas for priority implementation.

— Peter O'Donnell

EMA NOTES

GMP INSPECTIONS IN PORTUGAL

The mutual recognition agreement between the European Union (EU) and the US to recognize inspections of manufacturing sites for human medicines conducted in their respective territories has made further progress. In September, the FDA confirmed the capability of one additional EU Member State (Portugal) to carry out good manufacturing practice (GMP) inspections at a level equivalent to the US. There are now a total of 15 member states whose inspection results the FDA can rely on to replace their own inspections. Since November 2017, EU member states and the European Medicines Agency (EMA) can rely on inspection results from the FDA to replace their own inspections.

GENE THERAPY FOR RARE INHERITED DISORDER

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorization for the gene therapy Luxturna (voretigene neparvovec) for the treatment of adults and children suffering from inherited retinal dystrophy caused by RPE65 gene mutations, a rare genetic disorder which causes vision loss and usually leads to blindness. Luxturna is meant for patients with confirmed biallelic mutations of the RPE65 gene (i.e., patients who have inherited the mutation from both parents) and who have sufficient viable retinal cells.

MIGRAINE GENE THERAPY

CHMP has recommended granting a marketing authorization for Emgality (galcanezumab), a monoclonal antibody for the prevention of migraine. Emgality belongs to a new class of medicines that work by blocking the activity of calcitonin gene-related peptide (CGRP), a molecule that is involved in migraine attacks.

REGULATORY

EXPERTS LOOK TO UPDATE DIABETES STUDY REQUIREMENTS

An FDA advisory panel agreed last month on the need to streamline and simplify recommendations for studying the risks of cardiovascular events in new treatments for type 2 diabetes, but expressed a range of opinions on what specific changes to make in current requirements. Leading endocrinologists were split on what assessment is needed to detect any adverse signals of cardiovascular (CV) risk, and whether that involves premarket, postmarket, or both kinds of studies.

The main issue before the FDA Endocrinologic and Metabolic Drugs Advisory Committee at its October meeting was whether and how to revise a 2008 guidance that requires sponsors to conduct extensive outcomes studies on new antidiabetic therapies to ensure no unacceptable increase in CV risk to patients. In the decade since then, eight extensive and costly cardiovascular outcomes trials (CVOTs) have demonstrated no excess CV problems, and some indicate reduced risk for such problems (see bit.ly/2JvGZBK). This finding has led experts at FDA, academia, and industry to question the continued validity of the diabetes study requirements. Sponsors estimate that CVOT studies cost $200 million to $400 million each, greatly increasing the cost of development programs for new therapies.

Yet after two days of deliberations, the panel was evenly divided, with a scant majority voting to continue the current CVOT requirement. This group maintained that there is no substitute for randomized CVOTs, and that registries could not provide sufficient information. Those advocating for change maintained that it no longer is necessary to require outcomes studies, and that more robust premarket trials can better detect CV risk signals. Overall, there was strong support for a range of modifications to make the development of new diabetes treatments less costly and more efficient. Experts agreed that postmarket studies should be required only to further assess signals seen in premarket studies. And Phase II and III trials should be large enough to detect adverse signals and should be enriched to enroll patients with high CV risk.

Analysts have noted a decline in new programs for developing diabetes drugs since the 2008 guidance. FDA is expected to take note of the general consensus on the need to update its policy, most likely by recommending expanded premarket studies and reducing requirements for postmarket CVOT trials.

— Jill Wechsler

NEWS NOTES

CLINERION MOVES TO NEW HEADQUARTERS

The real-world data solutions company Clinerion is moving to new offices in Basel, Switzerland. Following expansion in its business, the organization is in the process of growing its global team. In the six months leading up to the start of 2019, Clinerion expects to have added several additional new positions. Staffing is increasing across areas such as customer solutions, site and patient network development, software development, data analytics, and marketing.

Clinerion's new offices have nearly double the floorspace of its old premises, matching the increased requirements of its expanding business. Though a new facility, the company's headquarters remain in Basel, where Clinerion analysts will look to tap into valuable insights from anonymized patient data throughout the company's network of hospital and data partners.

"Basel has critical mass in its life sciences ecosystem and an infrastructure which promotes a strong innovation culture," says Ian Rentsch, Clinerion CEO. "Here, we have the opportunity to interact with leaders of the industry on a close, daily basis."

NOVOTECH ACQUIRES CNS

Novotech, the Asia-Pacific-based CRO, has acquired Australasian CRO Clinical Network Services (CNS) as part of a mutual mission to expand services to biopharma for early phase product development and clinical research through to later phase regional and global trials. Both companies will continue to retain their separate brands and identities.

Novotech has more than 400 staff across Asia-Pacific and business development offices in the U.S. CNS has more than 140 staff in Australia, New Zealand, and the U.S.

As part of the deal, clients can access services from both groups, including the CNS BioDesk, which provides early stage product development advice, including toxicology, CMC and FDA/EMA regulatory consulting and interactions; and Novotech's advanced regional IT infrastructure, to support their clinical research programs. Early phase research in Australasia has seen solid growth over the last seven years, company executives said.

ORACLE NABS GOBALTO

Oracle has entered into an agreement to acquire goBalto, which delivers cloud solutions for clinical trials by streamlining and automating the selection and set up of clinical research sites to conduct studies.

NOVARTIS AND PFIZER COLLABORATE FOR NASH

Novartis has struck a clinical development agreement with big pharma compatriot Pfizer, which will include a study combining tropifexor and one or more Pfizer compounds for the treatment of nonalcoholic steatohepatitis (NASH). The financial details of the transaction were not disclosed.

NASH is a complex condition with no currently available treatment options. NASH presents a high unmet patient need, as it affects up to 6.5% of the population worldwide, and is largely asymptomatic.

— Staff and wire reports

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By 2020 NASH will be the leading cause for liver transplantation globally. However, stratifying and referring the right patients for clinical trials is a challenge; we know it is more common among people with type-2 diabetes and obesity, but that's not precise enough. And since the only definitive diagnostic tool for NASH is a liver biopsy, improved pre-screening is critical. The clinical complexities in NASH are also compounded by a lack of understanding of the full trajectory of patients – what are the early signs? What are the stages? Where do these patients interact with the system?

All of these challenges are converging to make NASH clinical trials uniquely difficult to deliver.

But a multi-faceted, data-driven approach early on can change the status quo. By building the right network model, better education programs, data-driven recruiting strategies, and more innovative diagnostic tools, IQVIA is leading the way toward new solutions.

4 Key take-aways:

When you join our webinar, you will walk away with:

- An overview a of the NASH landscape, including recruitment rates and how predictive analytics can accelerate enrollment
- Strategies to overcome the challenges associated with identifying undiagnosed NASH patients
- Methods available to enhance the screening process
- An understanding of how and when to develop a network approach to Real World Data

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For technical questions about this webinar,
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Risk-Based Monitoring Versus Source Data Verification

Penelope Manasco, MD, Eric Herbel, Sean Bennett, MD, PhD, Michelle Pallas, Lisa Bedell, Deborah Thompson, Kevin Fielman, PhD, Garrett Manasco, Charlene Kimmel, Everett Lambeth, Lisa Danzig, MD

Pilot study compares a risk-based monitoring and remote trial management method with traditional on-site source data verification for trial oversight.

RISK-BASED MONITORING

Five years ago, the FDA and the European Medicines Agency (EMA) released final guidance to change clinical trial oversight methodology from on-site visits using source data verification (SDV), the gold standard for more than 30 years, to a risk-based monitoring (RBM) approach.[1,2]

Implementing this guidance created two daunting challenges to reconcile as follows:

- No standard RBM definition or standard way to implement RBM exists; these myriad of definitions and implementation approaches correspondingly represent different levels of effectiveness to identify "errors that matter."
- No head-to-head comparisons exist that compare different trial oversight methods.

This lack of scientific data on trial oversight effectiveness is a critical unmet clinical research need. It affects more than 100,000 research participants per year and their healthcare providers.

This article represents a prospective analysis comparing the effectiveness of using traditional SDV versus one method of RBM (i.e., the MANA Method). We identified the specific RBM method used herein due to inconsistent RBM definitions and RBM implementation methods, and the varying levels of effectiveness for all the different RBM approaches.

METHODOLOGY

(Note: MANA RBM's approach is a patent-pending, data-driven, scientifically-focused, systematic, remote approach to trial oversight called the MANA Method. This approach, conducted independently of the EDC, synthesizes data across data sets and data sources to conduct review of protocol-specific high-risk data and processes identified during a proprietary, risk assessment service. This review focuses on how analysis and safety data are collected (i.e., process) in addition to the actual data for analysis. Integrated remote subject review starts within days of subject visits and includes rapid trend analysis of site performance to identify and correct systematic errors quickly.)

Research methods

PaxVax conducted a Phase IV vaccine trial in approximately 500 subjects at nine U.S. sites.

The study was conducted using electronic data capture (EDC). The trial was approved by an institution review board (IRB) and each subject signed an IRB-approved informed consent prior to participating. Subjects received one dose of the study vaccine. Participants collected any changes in health for nine days in a paper diary aid, and sites entered the results into the EDC. Each research site maintained its own informed consents and site regulatory binders.

Site monitors visited the research sites monthly and spent approximately 72 days on-site conducting SDV of the trial data. PaxVax's senior management team (i.e., medical monitor; senior director, biostatistics; director of data management and statistical programming) reviewed the data monthly to identify trends or data errors that would be followed up by the site monitor.

MANA RBM modified its risk-based monitoring and remote trial management system (i.e., the MANA Method) to initiate an RBM approach for this study that began after 5.5 months of trial conduct (approximately 500 subjects already enrolled). To fully implement the MANA Method,

additional trial oversight and remote document review, including informed consents and site regulatory documents, would also have been implemented and evaluated.

In this pilot study, MANA RBM independently and remotely reviewed and used the existing trial data available electronically to determine whether errors and trends could be identified faster and more comprehensively than using the traditional SDV method. Analysis of informed consents, regulatory documents, and source documents were not included in this pilot study because the documents were not available electronically.

MANA RBM first conducted a proprietary risk assessment service based on the protocol. It then designed proprietary study-specific reports and data visualizations to evaluate the high-risk data and processes identified during the risk assessment. The basic categories included: efficacy endpoints, safety assessments, investigational product (IP) management, and human subjects' protection.

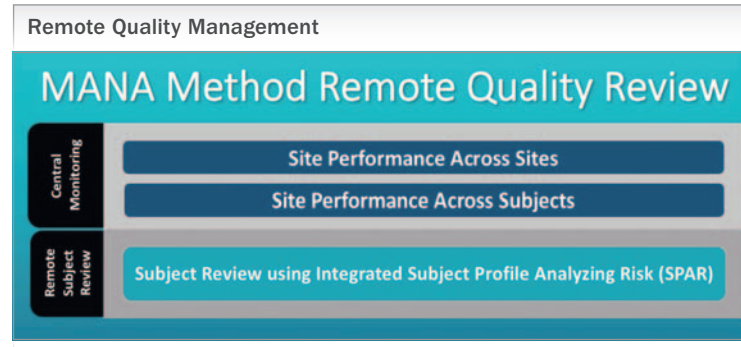
Trial data was imported from the EDC platform into JReview, hosted by Integrated Clinical Systems, Inc. MANA RBM designed its proprietary Subject Profile Analyzing Risk (SPAR) tool to provide an integrated visualization of the high-risk data for each subject over time and trained the remote monitors in its use. SPAR configuration is unique for each trial based on the critical issues identified during the risk assessment. Additional proprietary, custom reports were also developed to support protocol-specific analysis of high-risk data and processes and trends.

All review was performed independently of the EDC system and based on MANA RBM data analytics. Results of the review were captured in a separate, proprietary MANA RBM Site Tracker Analyzing Risk database (STAR); MANA RBM developed this tool to conduct study quality oversight. Subject review was documented in JReview.

MANA RBM conducted review using its remote quality management approach as shown in Figure 1. The MANA Method splits the review process into tiers. Remote site monitors focus on subject review and high-risk data and process oversight at the subject level. Central review focuses remote review on trend analysis by evaluating data across subjects at a single site and across sites.

The pilot study compared SDV versus the MANA Method in the following areas:

1) Identifying major deviations
2) Queries raised as a result of SDV
3) Identifying trends in data affecting trial conduct and/or results
4) Timing of the subject review
5) Resource use



Source: Manasco et al.

Figure 1. The MANA Method splits the review process into tiers.

Results

Risk assessment and development of protocol-specific reports: MANA RBM conducted the risk assessment and implemented the SPAR within two weeks of uploading the data into JReview. Additional custom reports were developed over eight weeks. These reports included customized, cross-database reports and trend analysis of high-risk data and processes.

Subject review: Once the SPAR was available, reviewers began reviewing the data immediately. MANA RBM split the subject review. An experienced monitor reviewed half of the subjects during the first month and the data reviewer, new to subject review, reviewed the other half of the subjects during that month. The following month, the subject reviewers switched subjects to review to allow evaluation of oversight by remote monitors with different training and experience. The lead monitor performed quality control (QC) oversight of each of the remote monitors to provide immediate feedback on items missed or documentation correction.

Identification of protocol deviations. MANA RBM's remote site monitors identified critical deviations using the SPAR and accompanying high-risk reports. The MANA Method identified critical deviations not previously identified by the sponsor's on-site monitors.

Speed of identification. Using remote methods, the monitoring team could have identified deviations faster and earlier than using SDV and on-site visits. Within six weeks, two rounds of review of all critical subject data were completed and all deviations for critical data were identified.

Categorization of deviations. Differences in classifications of deviations as major or minor were identified between the MANA RBM remote monitoring team and the on-site monitors. This resulted in challenges when comparing the total numbers of deviations. These totals were similar and there were no major deviations discovered by the sponsor's on-site monitors that the MANA Method did not also identify remotely.

Source document review: This study was conducted with paper memory aids and transcription by the research sites. Since this was a pilot study, sites were not asked to convert the paper memory aids to certified copies, which would have allowed remote review.

To evaluate whether there were findings that the MANA Method would not have been able to identify without on-site visits or using eDiaries, MANA RBM reviewed the queries related to subject diaries generated from the study. The MANA RBM team identified 300 queries associated with SDV. Table 1 (see page 10) shows the distribution of the queries and illustrates how remote review would have identified all critical findings with the use of eSource or certified copies of the diary aids. Important data is defined as data that would affect subject safety or analysis of efficacy.

MANA RBM reviewed the important data remotely from source review query rates and found that two sites had much higher query rates (i.e., 2-10 times the rates of the other sites), as shown in Table 2 (see page 10). This information, if known to the sponsor, would have

allowed it to determine the need for continued on-site SDV and, if needed, focus SDV, additional training, or other strategic considerations on only two sites instead of all sites.

MANA Method central review and trending

Central review and trending was conducted in addition to subject review. This review occurred during the second and third month of the pilot study using proprietary reports designed specifically for the high-risk areas identified in the study's protocol. From this review, MANA RBM central monitors recognized several trends that could have significantly impacted this study as follows:

1) Deviation evaluation identified at least one trend that could have enabled more evaluable subjects. A higher rate of out of window visits existed for one site. While not usually considered a major deviation, the timing of this critical visit represented the collection point for primary efficacy data. The MANA Method would have identified and corrected this error sooner, leading to more evaluable subjects. On-site monitors did not identify this issue. The PaxVax senior clinical research management team identified this site deviation at its monthly review meeting while the MANA RBM reviewers discovered this issue immediately upon performing central review.

2) A vital signs evaluation identified one site that had issues with collecting vital signs; specifically, collecting manual temperatures. Analytics identified this issue by using the differences in the mean values and a scattergram of actual values. This indicated a process issue that could have significant impact on future studies where immediate measures of temperature elevation after an IV injection could have been under-reported. Only the MANA Method remote central monitoring approach identified this issue.

3) Incomplete dosing represented another area where variability existed in performance across sites. Since sites "batch" (i.e., enroll large groups of subjects over a few days) their dosing for vaccine trials, identifying this issue rapidly may have increased the number of subjects that took the complete dose. The senior clinical research management team noted this issue at its monthly meeting. The MANA Method central monitors noted it immediately upon review. On-site SDV did not identify this issue.

4) Variability in reporting on adverse events of special interest occurred across sites. One site routinely ranked lowest or second lowest among the sites across the reported eight adverse events. While it was not clear if an issue existed, it was a trend that should have been evaluated to understand the processes by which this critical assessment was being conducted. Only the MANA Method central monitoring approach identified this finding. In Table 3 (see page 11), all sites with at least 15 subjects enrolled were evaluated on the ranking, across sites, for severity of the adverse events of special interest using z-scores (i.e., the number of standard deviations from the mean). One site routinely ranked subjects either the lowest or second lowest in severity, while one site routinely ranked subjects at a higher severity.

Findings not requiring action

1) The early termination rate was higher at one site than at the others. The reasons for early termination were not different across sites. No action was recommended at that time.

Distribution of Queries

ITEM	NUMBER	COMMENTS
Number of queries related to source	300	
Number of queries for important data	74 (25%)	Included questions related to IC time, Adverse events of special Interest (AESI) reporting
Number of AESI (missing) queried in the EDC[1]	12	All mild
Number of AEs (missing) queried in the EDC	1	Vasovagal reaction post-blood draw-marked as mild

[1] All 12 AESI would have been identified using an eDiary

Source: Manasco et al.

Table 1. Details of source document review.

High Query Rate Sites

SITE	NUMBER ENROLLED	# IMPORTANT FINDINGS-SDV	QUERY RATE-IMPORTANT FINDINGS
9	93	8	0.09
13	92	1	0.01
14	68	28	0.41
19	97	11	0.11
27	40	13	0.33
30	78	4	0.05
32	9	1	0.11

Source: Manasco et al.

Table 2. Variability in queries of important data identified by on-site monitors.

Review timing

The MANA Method enabled remote, comprehensive subject review of the high-risk data and processes to begin within two weeks of starting the project. No minimum data requirement was required to begin the review after a subject's visit data was entered.

Central trend analysis began approximately two weeks after remote subject review and identified additional data errors that could be corrected quickly. This rapid review could have eliminated errors in several aspects of study conduct as follows:

- Large number of out-of-window visits for critical assessments at one site
- Large number of incomplete dosing at two sites
- Confusion about the definition of diarrhea versus loose stools across sites (about 85 queries)

AE-Reporting Range

SOLICITED ADVERSE EVENT												
SITE	# TREATED	All	abd	dia	fev	hed	loa	nau	tir	vom		Sum
Site 13	92	1	4	2	0	1	2	1	1	1		12
Site 30	79	3	3	0	3	3	1	5	2	4		21
Site 19	101	2	2	4	2	2	3	2	3	6		24
Site 09	94	5	1	1	5	5	5	4	6	3		30
Site 14	68	4	5	3	4	4	4	3	4	5		32
Site 27	40	7	6	5	1	6	6	6	5	2		37

Site 13:	in 7 of 8 solicited AE categories, Site 13 had the lowest or second lowest z-score rank
Site 27:	In 6 of 8 solicited AE categories, Site 27 had the highest or second highest z-score rank

Source: Manasco et al.

Table 3. Variability in rates of reporting of adverse events of special interest (solicited events) across sites based on sites with at least 15 subjects.

- Errors in manual temperature measures
- Errors identified early facilitate site retraining, thus, reducing the future workload for sites and study staff.

Resource use

The sponsor assigned eight months of resources to the study as follows:

- 1.75 full-time-equivalent (FTE) data manager (DM), a lead DM, and a programmer (study conduct only).
- 3 FTE monitors, including a lead monitor (72 days of on-site monitoring).
- Senior management: four senior managers met monthly for four hours. Prep time for the meetings estimated as 40 hours per meeting. A second monthly meeting reviewed deviations. It took approximately 10 hours of senior management and data management resources.

MANA RBM used the following resources

Design, build, and validate study-specific reports in JReview: 2 FTEs for two months.

The reviewer ("monitoring") resources were much smaller than used in a traditional trial as follows:

- 1 data reviewer (100 hours)—review time averaged seven minutes/subject
- 1 monitor (100 hours)—review time averaged seven minutes/subject
- Central monitor (analysis) (20 hours)
- Quality control of monitor and DM performance (20 hours)

Time savings occurred in three areas

- On-site monitoring: Time to conduct subject safety oversight (on-site SDV versus monitor remote review) resulted in a savings of at least 83% of monitoring time, since only the on-site monitoring time was used for this comparison.
- Data management review-data oversight took 100 hours versus 1.75 FTE (630 hours for two months). When data are cleaner, errors corrected earlier, and central oversight identifies the critical data trends, the time to raise and close queries is significantly decreased. In addition, when central monitoring oversight was used, the time to create the materials for senior management review (40 hours per month) could have been significantly decreased.
- The 20 hours of central monitor review would have saved senior management over 60 hours per month. This results in approximately 1.5 weeks of savings for senior management per month.

Discussion

Increased quality, lower cost, and faster review times (including earlier detection of problems) represent the holy grail of trial oversight. The dogma was that you could only achieve two of the three. Using the MANA Method for remote trial oversight in this pilot study confirmed this is no longer true.

1. Quality—The MANA Method identified issues not seen using SDV. Its review focused on "errors that matter" that could affect trial outcome, not just traditional SDV point-to-point checking or identifying only data that did not conform to expectations (e.g., out-of-range values). Central (cross subject/cross-site) and remote subject review identified specific site actions that could be corrected rapidly, enhancing the number of subjects that could be evaluated and lowering the overall burden of trial management.

A second quality benefit of this RBM approach was the ability to perform and document QC remotely on each monitor/data reviewer's performance. This provided enhanced oversight not possible when all or most activities occurred at the research site. In 2013, MANA RBM reported on using remote review to perform a 10% QC review of informed consents on 788 subjects across 12 sites. This review took two days and required no travel.[3]

PaxVax senior management spent a significant amount of time evaluating trends, which the MANA Method identified with fewer resources and faster while conducting the monitoring/trial oversight. Many companies do not have the resources and/or make the

commitment PaxVax made to oversee the trial at this level. These findings confirmed that the MANA Method provided a cost-effective alternative for allocating senior management resources efficiently.

Using the MANA Method, monitors/data managers understood the critical data and processes and how they should be evaluated based on the data and document review guidelines. Instead of reviewing the subject's data in the electronic case report form (eCRF), whether doing transcription checking or just reviewing the eCRF, the MANA Method allowed more comprehensive oversight of each subject's data in context (i.e., across multiple data sets) and over time. This approach identified errors in process that were not obvious when the review focused only on out- of-range values, transcription errors, or missing data.

2. Time—The MANA Method meets the RBM regulatory guidance for rapidly reviewing critical data. The main tool used for subject review, MANA RBM's Subject Profile Analyzing Risk (SPAR), was built and deployed within two weeks of data upload into JReview—allowing comprehensive subject data review immediately after data entry.

While not possible in this pilot, when the MANA Method is implemented from the beginning of the trial, actual time to subject review and time to identification of major issues could be calculated, delivering oversight in days rather than waiting for an on-site visit.

This illustrates how overall monitoring time can be greatly decreased. Instead of selecting a subset of subjects or a subset of data for SDV, now every subject's critical data can be reviewed without impacting overall study costs. Rapid, comprehensive review can also occur when new data are added without significantly impacting costs. There is no "critical amount" of data needed to perform subject review. The data from a subject visit is sufficient to start review. These findings align with the data MANA RBM previously published on the speed of using the SPAR to conduct subject review.[4]

Once the MANA RBM protocol-specific complete reports were designed, developed, and validated, the actual review process was significantly shorter, and performed remotely. This provides tremendous potential savings for studies, such as oncology trials, that currently require on-site visits to review subject data, even for a single subject.

Time savings were not restricted only to monitoring time. Using the MANA Method, site monitoring savings were at least 83%, data management time savings could have exceeded 40 hours per month, and senior management time savings could have exceeded 60 hours per month.

3. Cost—This approach should be, at a minimum, cost-neutral. Cost savings can be significant depending on how the entire study is designed and implemented.

Any cost comparisons of methods should include total costs for trial oversight. With better oversight by the monitors, data are corrected faster—saving site time and enhancing the number of evaluable subjects. In addition, this pilot demonstrated that internal senior management time can be saved when the MANA Method is used to ensure cleaner data and identify critical issues earlier.

Using an electronic investigator site file (eISF) and certified copies of informed consent and other source documents would have enabled complete remote review because all documents would have been available remotely. Clinical trial associates can perform many tasks to manage the regulatory binders (i.e., complete and correct documents) and informed consent review—adding to cost savings. While the eISF and remote informed consent review were not used in the pilot, these tools can save additional resources and enable more comprehensive remote review.

Employing ePRO/eDiary in this study would have also yielded significant cost savings as discussed ahead. If eDiaries had been used, with eConsent (or certified copies of paper informed consents and subject diaries) and eISF, the number of on-site visits could have been significantly decreased.

The importance of eSource and eConsent

eSource and eConsent provide several benefits for RBM and remote trial management. Most companies incorrectly assume a change is necessary to add these tools to its EDC. eSource can be implemented using EDC with direct data entry or with a system designed to be used on a tablet. The benefits include:

- Meets the ICHE6(R2) and eSource ALCOA data requirements (i.e., Attributable, Legible, Contemporaneous, Original, Accurate).
- Immediate access to data for review.
- Collecting the data needed to document study processes, not just the clinical data needed for analysis.
- Identifying errors at the user level based on audit trail or documentation of who performed assessments, rather than just at the site level, allowing for more focused remediation.
- Providing immediate feedback to the person conducting the assessment through instructions and queries to identify data that do not conform to expectations (e.g., a very low height recorded because the height entry recorded was in centimeters but collected in inches).
- Using the audit trail to identify data not entered contemporaneously according to the protocol and instead entered post hoc.
- Providing a complete source record for each subject.
- Allowing remote QC of monitor/data management performance because all subject data are available for review.

Using eSource provides significant cost savings. For the 500+ subjects in this study, using an eDiary would have resulted in savings from sites entering 20,000 data points from memory aids (assuming 40 items/subject, five seconds of data entry/item), monitors visiting the sites to review the 20,000 data points (five seconds/item), and an estimated 500 queries (2.5% error rate, 15 minutes/query). This one change could have saved, conservatively, 179 hours of study staff time (over four weeks of work), not including costly monitor travel time or the increased frequency of visits required to review these critical data.

For eConsent, additional benefits include:

- Immediate access to the informed consent forms (ICF) for remote review.
- Assuring the correct ICF version was used.
- Importing the date/time of the ICF signature into the EDC/eSource system. This can be a triggering event to activate the EDC/eSource and assure that no assessments were done before completing the ICF. This feature is not available in all systems.
- Eliminating many edit checks and queries based on determining

the time of informed consent (if import of date/time into the EDC was used).
- Providing additional documentation of the process of obtaining informed consent.
- Remote audits of informed consents.

Using certified copies of paper informed consents and paper subject source data such as diaries provide an intermediate alternative to eConsent and facilitates rapid remote review.

The importance of central review and trending

While MANA RBM remote site monitors found important deviations using subject review, the central review process was invaluable in identifying the critical findings discussed in this article.

Reviewing trends allowed the MANA RBM team to identify sites having problems with scheduling patient visits, dosing according to the protocol, methods for collecting vital signs, and rating differences. While not necessarily critical findings in isolation, these issues can affect trial outcomes if left alone to compound over time. Investigating critical data and process findings represent the core of RBM principles.

Oversight should be focused on "errors that matter," which include processes in addition to analysis data. Trend analysis is critical because trends indicate systemic issues with those data and processes. These types of issues cannot be identified by SDV or even remote eCRF review. Only through using more scientific, data-driven, systematic approaches can important findings be identified, evaluated, and corrected.

Protocol-specific analysis

It is notable, for many reasons, that many RBM models incorporate SDV as its method for quality oversight; albeit fewer fields are now reviewed than the previous 100% SDV standard prior to the release of the FDA, EMA, and ICH Guidances. One problem reported in the Kunzi et al. paper is echoed by others: That monitors, although instructed to do less SDV, are concerned that they do not have a good grasp of the subjects when doing anything less than 100% SDV and will, therefore, perform 100% SDV regardless of the monitoring plan—this negated any anticipated RBM cost savings and required longer site visits.[5]

Our data conflict with the perceptions published by Kunzi et al., which reported that 58% of monitors in Europe, experienced in RBM, thought important protocol violations were missed using RBM.[5] The MANA Method identified remotely all critical deviations discovered by on-site monitors.

In addition, the MANA Method allowed the monitors to know exactly what the important data were and how to efficiently review all critical data in minutes, while providing more effective oversight than traditional SDV.

Sponsor opportunities

These data demonstrate the potential opportunities for enhanced trial oversight using remote, systematic, data-driven, analytic methods focused on the data that matters, (i.e., affecting trial analysis, subject safety, IP management, and human subject protection). These approaches use fewer resources, at a lower cost, and can be adopted without increasing study budgets—in many cases with lower study budgets. More importantly, trial quality is improved and sponsors know immediately about the issues that can affect the study, study participants, and regulatory submissions.

Just as sound research methods are the hallmark of pharma, biotech, device, and vaccine discovery efforts, sponsors now have the opportunity and the responsibility to apply sound, quality-based research methods and tools to the clinical research they conduct. As clinical research professionals, it is our responsibility to embrace improved methods for quality oversight and not be complacent and continue to perform trials "as we have always done them." Regulators, patients, and their physicians are counting on us.

The MANA Method is a proprietary, study-specific RBM approach performed remotely, independent of the EDC system used, and adoptable at any time during trial conduct. It was shown to systematically identify errors in trial conduct, subject safety oversight, and GCP compliance. The MANA Method identified critical errors in trial data and study conduct trends, within and across sites, more effectively when compared with on-site SDV. This pilot study demonstrated that subject review could be started earlier, and overall resource use was less than with traditional SDV on-site monitoring.

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The Basics of Clinical Trial Centralized Monitoring

Adam Beauregard, Vadim Tantsyura, Fernand Labrie

Examining the practicality of implementing CM techniques to drive trial oversight efficiency while saving on-site monitoring resources and costs.

PEER REVIEW

In the context of multicenter clinical research, centralized monitoring (CM) is the most efficient way to ensure patient safety, trial integrity, and data quality.[1-4] As it permits the study team to proactively detect anomalous data trends, CM improves the quality of the regulatory submissions with a direct impact on the time to marketing approval.

Since publication of the regulatory guidance on risk-based monitoring (RBM) five years ago,[5-7] the concept of CM has developed amid the emergence of technological enablers that make clinical research more data-driven than ever. Today, regulators encourage the use of CM in conjunction with on-site monitoring to oversee clinical trials.[8,9] Despite its unique potential for improving the quality of clinical trials, CM can appear so technical that sponsors often elect to renounce its use in favor of costly and less efficient traditional monitoring methods.[10]

In reality, only a few concepts that are relatively easy to master—and which most life sciences professionals are already familiar with—are required to properly implement CM.[11] In fact, to plan a CM strategy, one should be familiar with the concept of risk management, which involves identifying risks, estimating their potential impact, and devising efficacious mitigation strategies. Then, to perform CM, one needs to understand how simple statistics related to the means and the standard deviations can be used to detect outliers. Additional CM skills include the ability to detect scientific misconduct using the chi-squared distribution, which is closely related to the normal distribution.

The objective of this article is to show that performing CM is relatively easy and accessible to any research professional inspired by the objective of overseeing trials with optimal efficiency while simultaneously saving on-site monitoring resources. The central monitoring techniques presented in this article can be implemented using readily available tools such as Microsoft Excel.

Risk assessment and management

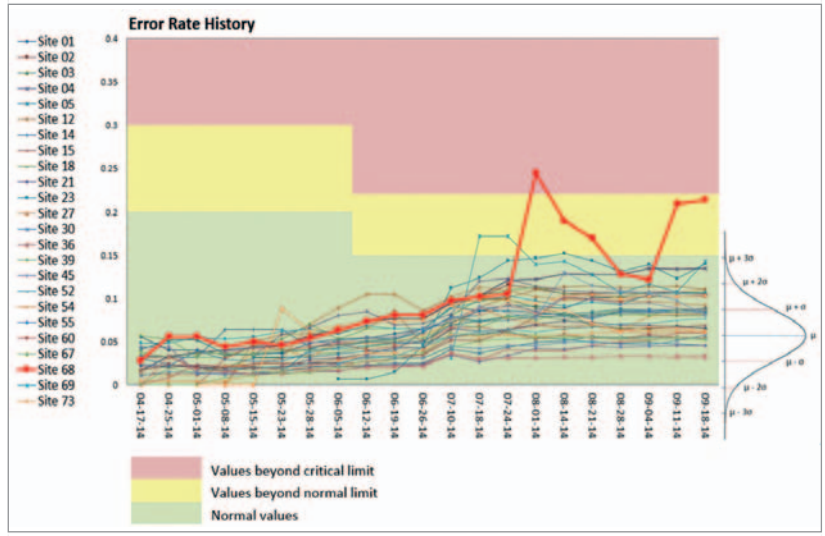
Because CM is a tool within a risk management process, central monitors must first understand how to identify and mitigate risks. A risk assessment, which is an integral part of a risk management process, allows one to identify a protocol's inherent scientific and operational risk factors, rate their respective potential impacts, and either eliminate them or develop risk mitigation strategies to control them efficiently. In the context of clinical trials, the risk assessment should focus on risks relevant to a subject's safety, the trial integrity, and the data quality. A proper risk assessment is especially important as regulators require that sponsors document the rationale for a chosen central monitoring strategy.[12]

Key risk indicators

Key risk indicator (KRI) metrics are risk-factor correlates that can be calculated from the data available, and they are identified during the risk assessment process. While KRIs provide quantitative information, they offer a view that may lack context. As such, qualitative information obtained from communication with on-site monitors and study coordinators represent key risk information that should be used in conjunction with KRIs for the proper analysis of risks and the choice of mitigation actions. The purpose of central monitoring is not only to measure and reduce risks but also to provide perspective to the processes under review so that the most effective control strategy can be adopted.

Each KRI metric has associated values corresponding to limits, also known as tolerance thresholds, which are determined during the risk assessment process. When site-specific metrics fall beyond set limits, the root cause should be analyzed by central monitors and mitigation actions, devised during the risk assessment process, implemented as necessary. Figure 1 illustrates how a typical site-specific KRI metric (ex. error rate) may differ from the rest of the population and fall beyond set limits, thereby triggering local specific mitigation actions. Figure 1 also illustrates how limits may be changed according to the observed values as a study progresses.

KRI Metric Limits



Source: Beauregard et al.

Figure 1. Typical site-specific KRI history and associated limits.

Risk importance

Using a risk matrix requires judgment for the probability of occurrence, the potential impact and the detectability of each risk factor, in order to generate a score that permits ranking the KRIs according to their importance. This method of assessing risks is used in the risk assessment categorization tool (RACT) published by TransCelerate BioPharma Inc.[13] It should be noted that the relative importance of each KRI does not influence the level of oversight on them but rather serves as a scale for the intensity of the mitigation actions put in place. For example, addressing a KRI of low importance that falls outside its normal limit may require nothing more than emails and phone calls to the site, whereas addressing a KRI of high importance that falls outside its critical limit may require more aggressive and resource-intensive approaches such as the dispatching of on-site monitors or the initiation of corrective and preventative action (CAPA) processes.

The relative risk importance changes as the study progresses. For example, the enrollment rate at the beginning of a study is an important indicator of trial viability, but after the enrollment is closed, it becomes only an indicator of high enrollers, which does not directly impact trial integrity. In comparison, a high query rate at the beginning of a study might be addressed by retraining research coordinators without significant consequences. But at the end of the study, it may directly impact study quality and the time to database lock. Accordingly, risk assessment should evaluate a study at different phases and the focus of risk management should change with time.

Table 1 includes the most common clinical trial KRIs and the typical output of a phase-relative risk assessment. Note that additional protocol-specific KRIs identified through a risk assessment process should be considered in different trials.

Central monitoring reports

Communication between different stakeholders is instrumental to the traceability of the CM process. The periodic central monitoring report should include the site-specific risk factors that are outside tolerance thresholds at the time of review, the specific metrics values, and their variations since the last review. To achieve a traceable central monitor-

Risk Assessment Output

KEY RISK INDICATORS	RISK CATEGORY			IMPORTANCE BY PHASE*		
	SUBJECT SAFETY	DATA QUALITY	TRIAL INTEGRITY	START-UP	EXECUTION	CLOSE-OUT
Enrollment Rate			✓	H	M	L
Screen Failure Rate			✓	M	M	L
Early Termination Rate	✓		✓	L	M	L
Out of Range Visit Rate			✓	L	M	M
Missed Dose Rate			✓	N/E	H	H
Missing Data Rate		✓	✓	H	H	M
Time to Data Entry		✓		M	H	M
Query Rate		✓	✓	L	H	H
Time to Query Resolution		✓		L	H	H
Error Rate		✓	✓	H	H	H
Deviation Rate	✓		✓	M	H	H
Adverse Event Rate	✓		✓	L	H	M
Site Appreciation Survey Score			✓	H	H	H

*L: Low, M: Medium, H: High, N/E: Not Evaluated

Source: Beauregard et al.

Table 1. Common key risk indicators and the typical output of a phase-relative risk assessment.

ing process, a concise analysis of the reasons why the outlying values are observed and the mitigation actions which are implemented in response should also be included in periodic reports. CM reports specifically serve to indicate how the situations progress in response to mitigation actions. Reporting frequency may vary from weekly to monthly depending on the data acquisition rate, which typically is higher during the study start-up period and lower during the close-out period.

Centralized monitoring: Statistical background

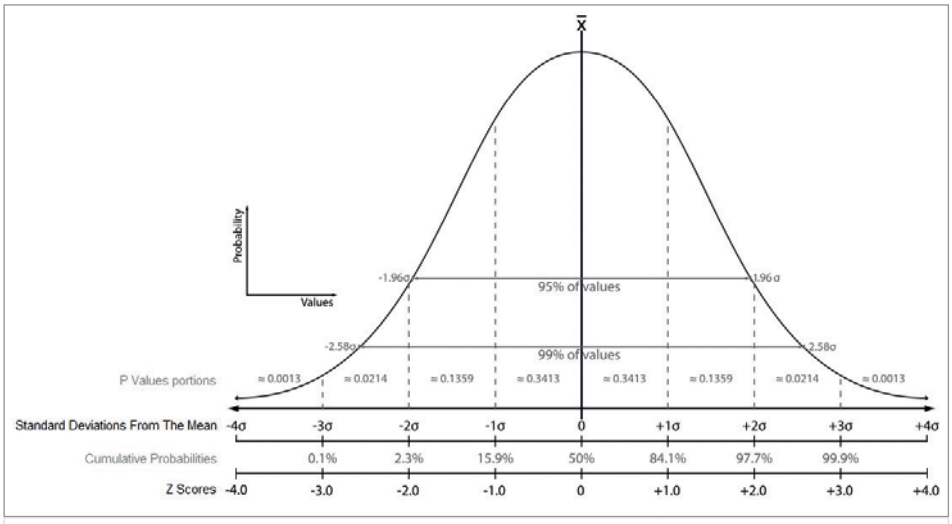
The FDA defines CM (aka "central statistical monitoring" or "statistical data surveillance") as *"a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted."*[14] Essentially, CM is used to perform the risk analysis part of a risk management process and involves performing calculations on an ongoing basis to discriminate normal from abnormal data. Today's technological enablers allow for the calculation of statistics from the accumulating data and it is thus essential for central monitors to be able to interpret the results correctly. The following sections cover the statistical notions that central monitors should be familiar with.

The normal distribution

The normal distribution is the most important concept in statistics and in order to evaluate the normality of calculated metrics, central monitors must understand its parameters—namely the mean and the standard deviation. The mean represents the anchor of normality and the standard deviation represents the stretch from the mean beyond which an observation may be considered relatively abnormal. Accordingly, the standard deviation and its multiples can be used to set tolerance thresholds, also known as outlier limits, beyond which an observation may be considered abnormal. It must be noted that judging what is normal and what is abnormal is a subjective endeavor, but the mean and the standard deviation remain the best parameters on which to base one's judgment. As described in the next sections, the mean and the standard deviation can be used to standardize observations as z-scores and the associated probabilities (p-values) of observing such z-scores.

Central monitors should take a moment to review Figure 2 and realize how the mean and the standard deviation relate to the z-scores and their p-values. The following section aims to clarify the implications of the term "normal," statistically speaking, in the context of multi-centered clinical research.

The Normal Distribution and its Parameters



Source: Beauregard et. al.

Figure 2. How the mean and the standard deviation relate to the z-scores and their p-values.

The z-score and p-value

The z-score corresponds to the number of standard deviations an observation is from the population mean. It is calculated as follows: $Z = (\chi - \mu) / (\sigma / \sqrt{n})$ where χ is the value for which the z-score is calculated, μ is the population's mean, and σ is the population's standard deviation, while n represents the sample size that corresponds to the number of observations made to compute the sample mean (e.g., a subject's mean blood pressure). When calculating a Z-score for a single observation (e.g., a site-specific KRI), n=1 and, therefore, $Z = (\chi - \mu) / \sigma$.

Once standardized as z-scores, the observations can easily be compared to the mean and to each other. Namely, Z-scores have associated p-values that can be used to judge the normality of the observed values. The z-score p-value is the probability of observing a value equal or more extreme than the value actually observed (χ), by chance alone and assuming that the population from which the value was obtained is normally distributed. The smaller the p-value, the less likely a person would be to observe a value "as extreme" as the one observed.

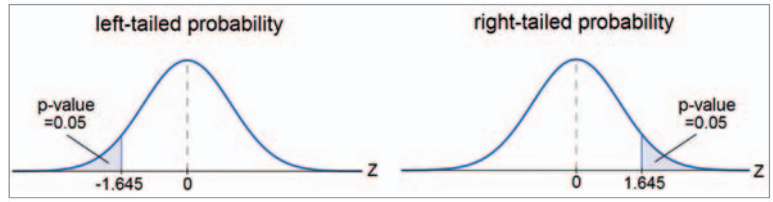
The z-score and p-value are very useful in the context of identifying outliers in clinical research datasets. Statistical software, including Excel, can be used to obtain p-values that correspond to the probability that an observation would be smaller (right-tailed p-value), or larger (left-tailed p-value) than an observed value. Figure 3 illustrates common scenarios.

The cumulative probability

The cumulative probability corresponds to the left-tailed probability of observing a value as small as, or smaller than, the observed value. As such, the smaller the cumulative probability, the further to the left of the population an observation is. On the other hand, the larger the cumulative probability is, the further to the right of the population an

observation is. For example, if a site-specific KRI metric value corresponds exactly to the population KRI mean value, its associated cumulative probability will be 50%. If another site-specific metric has a cumulative probability of 100%, it means that approximately 100% of the other sites' metrics values fall below the KRI value of that site and as such, it is safe to call it an outlier. In the context of central monitoring, the cumulative probability is particularly useful because outliers are often observations that are greater than the rest of the population.

Common Probability Scenarios



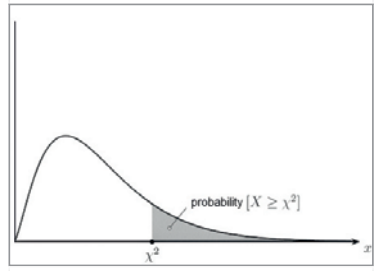
Source: Beauregard et al.

Figure 3. P-values associated with the z-scores of the normal distribution.

Fraud detection

CM should not be limited to the monitoring of KRIs. Other methods, such as the ones presented ahead, should be used to detect scientific misconduct. Deliberate data fraud is rare but can have significant impact on trial integrity. One straightforward way to fabricate data is to take existing data and copy them within or across study subjects. Such a data propagation method results in certain values occurring more often than others; a simple way to detect this type of data fabrication is to calculate the frequency of each observation. As such, frequency analysis can effectively detect if vital signs taken from only one subject were copied into two subjects' charts or if a single blood sample was split into two before being sent to the laboratory. In most cases, however, fraudsters are unlikely to be so careless as to copy data without modifying some of the values. Fortunately, there are other ways to detect fraud, which are harder to evade given the predictability of human nature.[15,16]

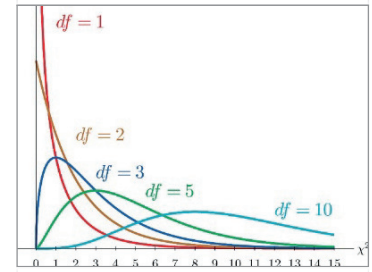
Observed vs. Expected Values



Source: Beauregard et al.

Figure 4. The chi-square distribution and associated right-tailed probability (p-value).

Shape of the Distribution



Source: Beauregard et al.

Figure 5. The chi-square distribution shape variations according to the degrees of freedom.

The chi-square distribution

The chi-square distribution is graphically different from the normal distribution, but it can be used in the same manner to assess the normality of values that follow its distribution pattern. Importantly, the sum of squares, which is defined as the squared differences between observed values and expected values, follows a chi-square distribution.[17] The chi-square statistic (χ^2) can thus be used to evaluate the difference between what is observed and what is expected as being normal. It is calculated as follows:

$$\chi^2 = \sum \frac{(Observed - Expected)^2}{Expected}$$

Like the z-score, the χ^2 statistic has associated p-values. Figure 4 shows how the χ^2 statistic (right-tailed p-values) corresponds to the probability of observing a difference between the observed and the expected values that would be as large or larger than the actually observed difference. The larger the χ^2 p-value, the closer the observed values lie from the expected ones. On the other hand, the smaller the χ^2 p-value, the farther the observed values will be from the expected ones. The degrees of freedom (DF) of the chi-square distribution correspond to the number of observations taken into account in the calculation of the χ^2 value. Figure 5 shows how the shape of the χ^2 distribution changes according to the degrees of freedom. Note that the degrees of freedom also correspond to the mean chi-square value for the different χ^2 distributions.

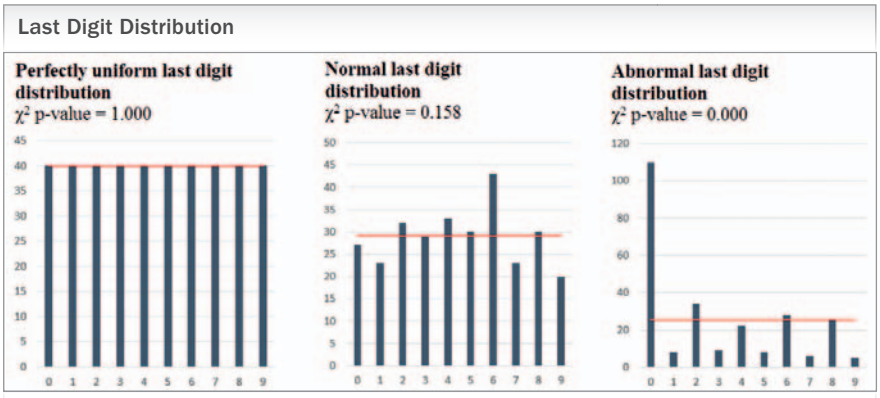
Because expected values are based upon calculated averages and real data never lie too close or too far from the expected values, the χ^2 p-value may indicate fraud if it is either too small or too large. Indeed, counterfeiters are bad at mimicking the randomness of nature[18-22] and when one observes data that are either too far or too close to expectations, it is reasonable to suspect fabrication. As described ahead, terminal digit analysis and inlier analysis are two types of analyses that use the χ^2 statistic to evaluate if data lie too far or too close to the expected values, respectively.

Too far from expectation: Terminal digit analysis

If we consider measurements that have two or more digits, we are expecting the frequencies at which the digits from 0s to 9s appear in the rightmost position to be approximately equal. To perform terminal digit analysis using the chi-square "goodness of fit" test with the χ^2 formula indicated at left, the *observed* values correspond to the number of times each digit, from 0 to 9, appears in the dataset of interest while the *expected* values for each digit corresponds to the number of measurements taken into account divided by 10, since each digit is expected to appear with equal frequency. The degrees of freedom associated with the terminal digit analysis is 9, considering the sample size of 10 possible categories (digits 0 to 9) minus 1. The calculated χ^2

p-value indicates the "goodness of fit" between the observed last digit distribution and a perfectly uniform last digit distribution.

Figure 6 illustrates how the χ^2 p-value relates to the last digit distribution. Note that if certain digits appear in the terminal position more often than others, it might be caused by measuring instruments or by normal practice that requires rounding.[23] In other cases, it might be because of fraud, as humans tend to favor certain digits when fabricating numbers.[24,25] The latter instance constitutes reprehensible behavior that has significant impact on the trustworthiness of all data provided by the site of interest.



Source: Beauregard et al.

Figure 6. Examples of last-digit distributions with their associated χ^2 p-values.

Too close to expectations: Inlier analysis

Real subject-specific data are expected to vary to a certain extent from one physician's office visit to the next. An inlier analysis can be used to detect whether this is the case or not. A single fabricated variable—let's say heart rate—may remain plausible on its own, but if considered with other fabricated variables such as respiration rate, systolic BP, diastolic BP, and temperature, the combined data are likely to exhibit an abnormal multivariate pattern that can be detected statistically.[26,27] Inlier analysis specifically evaluates how close to their respective means a set of multivariate observations lies and suggests fabrication if those observations, taken together, lie abnormally close to their respective mean. Specifically, if a subject's data have been chosen to mimic real data, its measures will consistently lie close to an anchor value,[28] such as the population's mean, and the sum of the differences between its observed measures and the population means for those measures will be smaller than the sum of differences calculated for the rest of the population. The sum of squared z-scores follows a chi-square distribution and it can be used, in place of the χ^2 statistic, to obtain p-values corresponding to the probability of observing a given sum of squared z-scores.[29] The following steps describe how to perform a multivariate inlier analysis:

- **Step 1.** Choose the variables to evaluate. In the context of clinical research, variables that can be easily fabricated include physical examination and vital signs data.
- **Step 2.** Calculate subject-specific z-scores for each variable using subject-specific mean scores (χ), population`s means (μ) and population standard deviation (σ) using $Z = (\chi - \mu) / (\sigma / \sqrt{n})$ where n represents the number of subject-specific samples used to calculate subject-specific means χ.
- **Step 3.** Square those z-scores and add them up to have subject-specific summed Z^2 values. Subject-specific summed Z^2 values should follow a χ^2 distribution with a degree of freedom corresponding to the number of variables considered in the calculation of the subject-specific summed Z^2.[30-33] An inlier can be identified as a subject with an unusually small summed Z^2 value and an associated p-value can be obtained using the subject-specific summed Z^2 value as a χ^2 value.

To visualize the inlier analysis, one can graph all subject-specific summed Z^2 values as cluster points along with anchor points corresponding to the number of variables taken into account for the calculation of the subject-specific summed Z^2 values (the degrees of freedom). As stated, the degrees of freedom represent the mean summed Z^2 value and this value corresponds to the normal distance from their respective means. Inliers will be apparent on such graphs as points that lie unusually far to the left from the mean summed Z^2 value, relative to other subject-specific summed Z^2 values. For better visualization, one can transform all summed Z^2 values using natural log function.

In Figure 7 (see facing page), the subject-specific natural log of summed squared z-scores were calculated using five variables, including heart rate, respiration rate, systolic BP, diastolic BP, and temperature. The normal distance from the multivariate mean is indicated by the red dotted line that corresponds to the natural log of the degree of freedom. The graph indicates that two subjects at site 17 and 18 have measures consistently close to their respective means. With such a scenario, central monitors have good reasons to inquire further with the site staff as to why those subjects' measures are so close to their respective means.

Limitations of CM

It is important to consider that there is no single universally applicable or generic outlier detection approach[34-36] and a direct confirmation of discrepancy or proof of fraud is seldom obtained from statistical evidence alone. Abnormal data analysis only serves as support for further investigation. In addition, because statistical power is dependent on sample size, it is important to consider that a large amount of false positive signals may be observed when the data sampled is small, such as is the case at the beginning of trials or when trials are of small size.[37] Thus, site-specific metrics should always be interpreted with the consideration of sample size. One may elect to wait for a sufficient amount of data to be accumulated at a site before initiating analysis for that site. Considering these limitations, CM should not rely only on statistical algorithms. Simple analysis such as checking if examination dates correspond to weekend or holiday dates can serve the purpose of flagging suspicious sites.[38,39] Also, the fact that a given site does not

Vizualizing Inlier Analysis

Source: Beauregard et al.

Figure 7. Subject-specific natural logs of summed squared Z^2 scores.

manage to generate enough data to be considered for analysis may constitute a signal in itself.

Conclusion

The core objective of CM is to support a risk management process that aims to ensure subjects' safety, trial integrity, and data quality in the most efficient way. CM can undoubtedly play an important role in increasing the quality of clinical trials as it allows sponsors to intelligently decrease the amount of costly on-site monitoring. This is very important since the overall cost of monitoring can represent up to one-fourth of trial costs[40-42] and the efficiency of monitoring efforts, including on-site and central monitoring, has a direct impact on the cost of clinical trials and the price of treatments that ensue. Abnormal data patterns can be readily detected even by simple statistical methods, and the skills required to perform CM do not necessitate extensive training nor the most advanced technology. In fact, most clinical research professionals have already been exposed to the statistical notions covered in this article and can carry on the task of CM with readily available tools such as Excel.

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Closer Pharma-Diagnostic Collaboration is Key to Alzheimer's Drug R&D

Pharmaceutical and diagnostic companies should design a long-term strategy to turn science and data into actionable medical innovations.

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Medical Director of Neurology, Quest Diagnostics

Since the turn of the decade, pharmaceutical and diagnostic companies have collaborated more than ever before to advance the commercial and clinical value of precision medicine. Today, the need for these collaborations is greater than ever before, as healthcare tackles one of medicine's greatest challenges: Alzheimer's disease (AD). According to the Alzheimer's Association, more than 5.7 million Americans live with AD, and the number is projected to increase to 14 million by the year 2050.

Tragically, AD remains virtually untreatable. Currently available medications have limited impact on progression and virtually no impact on the disease's severity.

Several barriers have stymied successful research and commercialization of drug targets. In fact, despite a drug pipeline with more than 100 treatment agents, not one drug has been approved to treat the underlying cause or slow the progression of AD since 2003. A 2018 analysis of Alzheimer's drug development published in *Translational Research & Clinical Interventions* noted that eight agents listed in Phase III in 2017 failed in clinical trials. Six drugs listed in Phase II last year are no longer in development, and trials for five particular agents in Phase I in 2017 were either completed or terminated and are not listed in the 2018 pipeline.

However, recent announcements from regulatory bodies and public health organizations offer great hope that promising new therapies can be accelerated through trials and approvals to the point of clinical care.

In April, the National Institute on Aging and Alzheimer's Association (NIA-AA) released a new research framework that proposes the use of biomarkers to assess the presence of AD, whether symptoms are present or not.

While not currently intended by clinical use, this new framework is expected to build upon research discoveries that certain biomarkers are predictive of AD by as much as 20 years. Specifically, the NIA-AA "biological construct" proposes to use three general groups of biomarkers—beta-amyloid, tau, and neurodegeneration, or neuronal injury (AT(N))—in a new AD classification system that covers the continuum of the disease.

The NIA-AA framework comes on the heels of the FDA's draft guidance in February on using biomarkers in an approval pathway for new AD drugs if drug developers could hit acceptable biomarkers that indicate the drug is working.

Taken together, these developments could lead to an improved understanding of the disease process and the sequence of events that lead to cognitive impairment and dementia—and an entirely new way of accurately measuring clinically meaningful cognitive and functional outcomes based on biological data. Most of all, they hold the potential to advance AD drug R&D and potentially surmount the many barriers to success in this area.

But the use of biomarkers in AD research will also require new types of collaborations by pharmaceutical companies and R&D partners—including diagnostic providers. While the new framework does not recommend the use of current biomarkers for clinical applications, some specialists today order them as clinical tests to enhance their assessment of patients. As a result, diagnostic providers specializing in AD, cognitive impairment, and dementia likely already perform these biomarker tests and may have vast data sources on which to glean insights useful in research settings.

AD drug research is a long-term game. In order to minimize risk and optimize a smooth and successful transition from lab discovery to clinical trial to regulatory approval, pharma and diagnostic companies should design a long-term strategy to turn science and data into actionable medical innovations. These include, potentially, companion and complementary diagnostics for future AD therapies. Here, a diagnostic provider can help generate the right data to support regulatory approval and payer support post-market launch.