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HS

Applying Quality Improvement to Clinical Trials

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Integrated Clinical Analytics Model to Improve Business and Operational Excellence in Clinical Research

Innovation and technology are driving efficiency and performance in clinical research by changing the way data are captured, monitored, analyzed, and reported. Mobile and Internet-connected medical devices generate large volumes of data in an environment where data science, data discovery, and visual analytical tools are empowering clinical researchers and study teams to improve trial management, trial monitoring, and trial performance.

PEER REVIEWED

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Over the years, contract research organizations (CROs) have built multiple applications using a variety of technologies to address the unique needs of their customers. Legacy applications lack integration, lack access to a single source of truth, and do not provide actionable information to improve the efficiency of trial conduct. Disparate systems containing redundant and inconsistent data are a major challenge for study teams trying to make the right decision at the right time on various business, operational, and clinical issues.

In addition to legacy application challenges, the complexity of studies can dramatically increase with the introduction of the "medical Internet of things" (MIOT)—an ecosystem of integrated infrastructure connecting people, processes, data, and medical devices to capture and process health-related data or to provide health-related services. MIOT devices generate a large volume of data, and some of the critical datasets need to be processed in real time.

Real-time data capture and validation reduces manual data entry errors and improves overall data quality and accuracy. Though wearable devices and other automated forms of data capture technologies are improving, they still lack integrated workflow to extract structured and unstructured data and to validate and transform data into a meaningful form for further analysis.

This paper discusses clinical trial challenges and the need for analytical tools, and proposes an integrated clinical analytics model to improve business and operational excellence.

CLINICAL TRIAL CHALLENGES

The high cost of research and numerous rules and regulations put the drug development industry under pressure to conduct clinical trials effectively and efficiently. A clinical trial is a scientific process leveraging other practices, including project management, manufacturing, and supply chain management. A recent report from Battelle states that "In 2013, the biopharmaceutical industry alone invested $10 billion in clinical trials, with a total reported 1.1 million patients enrolled—or approximately $9,090.91 spent per patient."[1]

Because of a high level of investment, compliance needs, safety concerns, and security guidelines, organizations depend on data-driven analytics to improve decision-making and prevent potential future issues.

NEED FOR ANALYTICS

An analytics solution provides unique insights, generates new knowledge, and improves outcomes. To optimize performance and improve decision-making, data-driven analytics should focus on standardization of datasets.[2] Organizations use analytics for business improvement, cost reduction, and customer experience improvement. For example, by combining analytics with manual efforts, one health system could reduce audit expenses by 75%.[3]

Traditionally, data managers and study teams identify data quality issues by analyzing the data during certain milestones or at the close of the study. This approach delays the process of addressing data quality, safety, and other critical issues to later in the study. Analytics combined with machine learning could allow for better insights and improved predictability.[3]

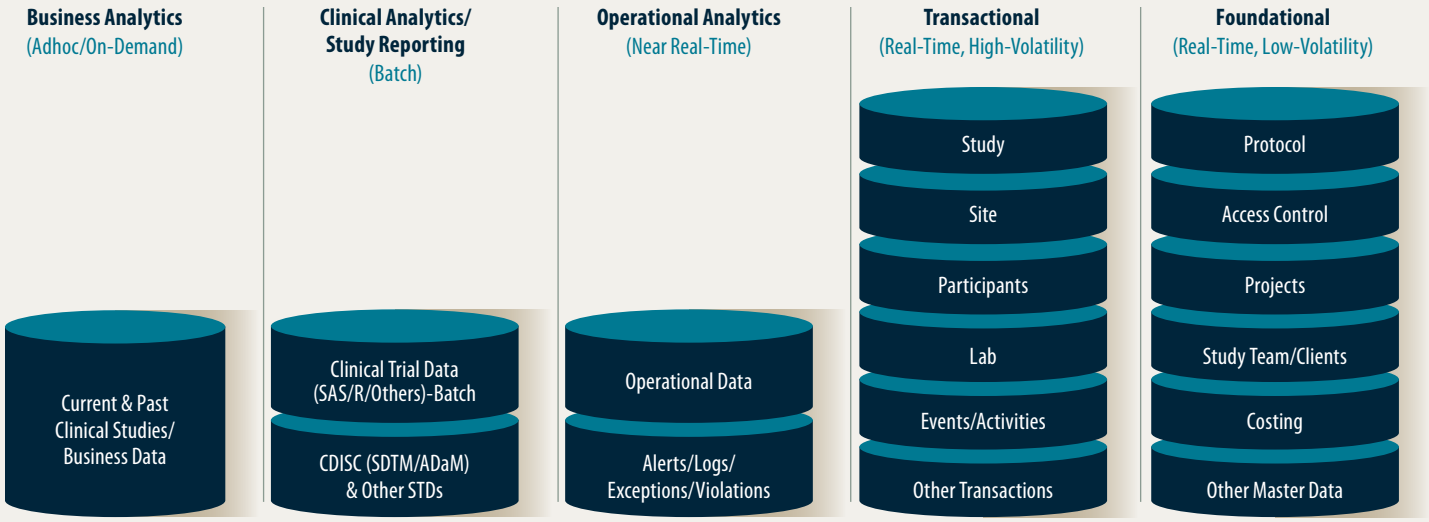
A 1999 report by the Institute of Medicine (now known as the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine) stated that medical errors each year take about 98,000 patient lives and cost hospitals nearly $29 billion.[4] This report also cited that three out of four errors could be eliminated by centralizing and integrating information, and by improving the availability of information about drugs and patients when needed.

Analytics are used for predicting patient health and for gaining insights on related areas like fraud detection, communication, and education. However, gathering and processing data for analytics poses challenges that are both qualitative and quantitative.[3]

Organizations are collecting more data about patients, and the rate of collection increases with personalized and MIOT devices. These data could be used to find simple and complex relationships, and the analysis could help to improve patient care, to prevent medical malpractice, to increase healthcare efficiency, and to support insurance and payments. Further, advances in technology and systems have generated a large volume of health data.[5] Analytics solutions empower healthcare professionals to improve clinical decision-making, predict risks, monitor patients, and manage finances.

Real-time data capture and validation reduces manual data entry errors and improves overall data quality and accuracy.

FIGURE 1: Data Architecture



Because of a high level of investment, compliance needs, safety concerns, and security guidelines, organizations depend on data-driven analytics to improve decision-making and prevent potential future issues.

DATA TYPES AND STORAGE

Visual analytics use interactive visual interfaces to gain insights from complex and large datasets that are processed on a near real-time basis. This can also be used to build dashboards for monitoring various health factors, guidelines, and compliance.[3] However, organizational data are going to be distributed and stored using different types of technologies. Further, data entities are represented using a variety of standards that may not be consistent with unified reporting and analytics.

As shown in Figure 1, clinical research data can be classified into a variety of functional areas in terms of their foundational, transactional, operational analytics, clinical analytics/study reporting, and business analytics purposes. In addition to the sources of data in these areas noted in Figure 1, some study leaders may also use external databases, social media, and other market sources to compare their data to data from the overall industry or specific competitors.

ANALYTICS TYPES

The following five different types of analytics may be used in clinical research:

1. **Transactional Analytics:** Clinical trials depend on many different types of applications, and on interactions with various internal and external users to capture and process data in real time. Transactional analytics focus on data at the transaction level; this type of analytics processes records in real time to improve specific outcomes. Clinical data managers can leverage transactional analytics to gain deeper insights on transactional data to improve quality by applying consistent business rules and policies.
2. **Operational Analytics:** This is the next level of transformation from traditional business intelligence. Operational analytics is a complex analytics process that consolidates various operational data sources to provide insights on current operations.[6] Clinical research associates, clinical project managers, and principal investigators can use operational analytics to support decision-making and improve implementation and monitoring of clinical trials. This includes application to such tasks as site selection, monitoring site performance, patient recruitment, drug distribution, managing payments, and scheduling.
3. **Clinical Analytics:** This helps researchers to compare current clinical study data to those from similar studies conducted internally based on therapeutic or domain-specific research. In addition, current data could be compared to past clinical trials data to predict or improve safety, efficiency, and efficacy of new medicines.
4. **Predictive Analytics:** Implementing predictive analytics requires current and past data related to studies conducted within an organization, plus additional relevant data from external and industry sources to model and predict certain types of events. Predictive analytics is a valuable tool for researchers to run trials effectively and improve key aspects of clinical research by unifying current and historical data to predict future events, prevent failures, and prescribe certain actions.

5. **Business Analytics:** This helps to run the business operations efficiently by using available time, budget, and resources. It also facilitates decision-making to improve and grow the business by analyzing challenges and opportunities in managing clinical trials. This includes gathering insights on Time, Cost, Scope, Human Resources, Stakeholders, Quality, and Risk Management. Business analytics could also be used for portfolio analysis by grouping together a similar set of related projects and focusing on high-risk project and related metrics.

INTEGRATED CLINICAL ANALYTICS MODEL

The use of analytics leverages existing organization data at various levels and provides value and insights for better operational planning and management. It requires an understanding of current operations and uses insights to improve performance and efficiency. To implement an analytics solution, organizations should create a consistent framework and take into account organization culture and policies. Further, analytics programs should be implemented incrementally, to avoid any potential disruptions to existing operations and customer impact.[7]

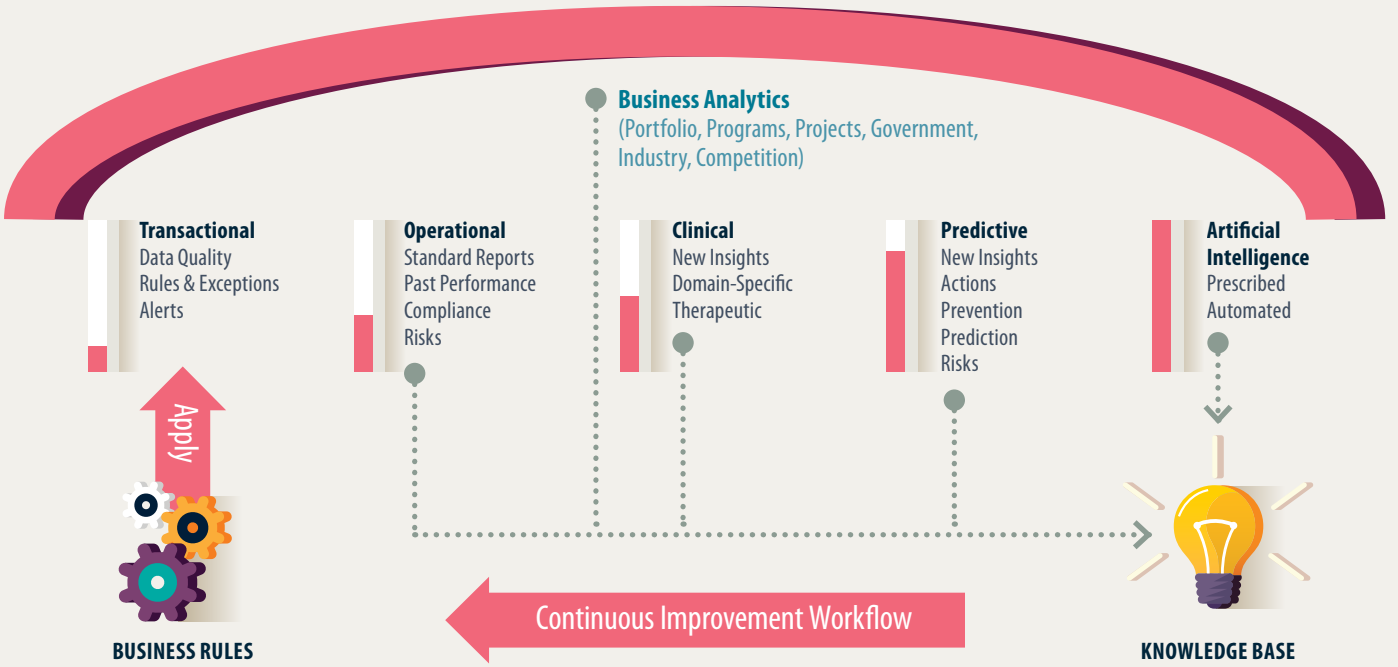
The proposed integrated clinical analytics model (ICAM) shown in Figure 2 will segment data analysis into multiple levels, with each level having a different purpose, scope, and focus area. The goal is to "learn fast and learn often" on various business, operational, and clinical functions.

The framework of this model is to learn using analytics, transform learnings to build a knowledge base, and use the knowledge base to create business rules and policies to govern and integrate with existing systems and processes.

The proposed ICAM will directly help clinical project managers, clinical research associates, study coordinators, and principal investigators measure, analyze, and improve study outcomes. Some of the applications are:

- Improve site feasibility and site selection based on past performance
- Improve site monitoring rules based on specific risks
- Improve patient engagement based on current performance, behavior, etc.
- Improve data quality on based on trends, control limits, etc.
- Improve supply chain logistics for drug distribution

FIGURE 2: Integrated Clinical Analytics Model (ICAM)



Empowering business with a highly sophisticated tool without proper governance may result in multiple dashboards, redundant and inconsistent datasets, uncontrolled data access, and unintended privacy and security issues.

IMPLEMENTATION STRATEGY

Implementation of this model involves dividing analytics solutions into multiple levels based on focal areas, systematically transforming learnings to build a knowledge base, and creating a workflow to apply the learnings to augment existing business rules, policies, checks, and audits.

Business processes are highly complex, and many organizations depend on information technology (IT) to identify, define, and manage rules digitally to achieve business goals and objectives. This includes defining and implementing business boundaries, business rules, policies, and regulations to conduct business efficiently.

A business rule is a means of managing various types of business domains and their components; it is a set of defined activities, rules, and constraints integrated with the business process workflow.[8,9] To gain insights on patient information, data residing in various places and different types of formats need to be consolidated into one repository.[10] This will help to predict and avoid various risk factors, including patients' compliance with appointments and medication schedules, and other behaviors during participation in trials.

Data preparation is one of the foundational processes in implementing any analytics solution. The first step is building a standard data dictionary for analytics by analyzing existing data sources. This is a collaborative effort undertaken with data stewards from different business functions, data architects, and development teams. Ideally, this effort should focus on a so-called "single source of truth," and avoid using secondary data which might have been transformed for other purposes or modified for individual use.

The second step is data mapping from source to target by using associated transformation rules. This is a critical step of the process to ensure that consistency is applied for similar datasets and that all business rules for transformation are consolidated into one place for review and applied for future changes.

The final step is grouping data to build a unified dataset based on the type of analytics and audience. One way of grouping data is based on business, operational, and clinical focus areas. The next section discusses common challenges of implementing an analytics solution.

IMPLEMENTATION CHALLENGES

Analytics implementation is a transformational program impacting people, process, and technology. As described below, implementation faces challenges relating to the areas of Data, Privacy, Security, Validation, Governance, Training and Development, and Outcome.

Data: Creating a unified data analytics model is a complex process. The widespread distribution of data using multiple technologies, along with nonstandard and unstructured data, poses technical and process challenges in implementation. Communicating overall vision, strategic objectives, and business outcomes to all stakeholders and building a business-IT partnership will help to reduce resistance and build support to standardize datasets owned by various business functions of the organization.

Privacy: Analytics provide wider connectivity and deeper insight on multiple data sources. Users can filter from large datasets and narrow down to specific data, which may expose personal identity or provide more information of a patient taking a specific type of treatment. Organizations should implement governance and review process on data standardization, data access, and controls on privacy-related exposure and risks.

Security: Analytics solutions should be carefully evaluated for integrated identity and access management policies to ensure that authentication and authorization are consistent with the rest of the systems in the organization. If the analytics solution includes data from electronic health records and personal health information, fine-grained access control needs to be implemented to govern and control access to these sensitive data. The system should be built with sufficient auditing and alerts to prevent any improper or fraudulent use of personal information beyond the intended use.

Validation: Modern analytics tools are shifting from IT-led to business-led solutions. Proper governance and validation on data and processes should be built to ensure consistency, quality, and accuracy. Scripts to extract, transform, and load data should be validated for compliance with 21 CFR Part 11 (Electronic Records; Electronic Signatures) of the *Code of Federal Regulations* on data extraction, data transformation, system and change controls, and other guidelines.

Governance: Analytics empowers business leaders to perform their own analyses by unifying diverse sets of business and operational data. Business teams need to work closely with IT to

understand data source, usage, security, and access. This will ensure that a consistent process is followed from data extraction, transformation, and exposure. In addition, proper governance should be in place for adding new data sources and allowing audit trails, for sharing data, and for generating custom dashboards.

Training and Development: Analytics teams need skilled resources with a good understanding of business and industry, data sources, data entities, and data usage. Having a well-trained workforce is one of the challenges organizations face while implementing big data analytics solutions.[11] The organization should perform a good skills assessment and fill the resource gaps with training or by recruiting external sources with experience in executing similar projects.

Outcome: Creating an analytics solution requires a high level of investment, and implementation may run from many months to years. Executing projects with agility by dividing large requirements into small chunks will help business teams to understand the need, measure the outcome, and realize the incremental value of the project goals and objectives.

RECOMMENDATIONS AND DISCUSSIONS

This paper provides an analytics model, approach, and implementation strategy to transform learnings and insights to improve productivity and performance. Implementation of this model requires identifying the unique needs of an organization and understanding its current processes, data, and systems. Empowering business with a highly sophisticated tool without proper governance may result in multiple dashboards, redundant and inconsistent datasets, uncontrolled data access, and unintended privacy and security issues. For successful implementation, organizations should create a sustainable review and governance process, including paying attention to data governance, data standards, data security, and extensive training on various tools and technologies used in analytics.

CONCLUSION

Modern clinical research depends on analytics to improve decision-making and gain insights on business and operational performance. This article has discussed the challenges and needs surrounding analytics in clinical research, looked at various analytics types, and presented the ICAM to transform insights gained by individuals into institutional knowledge. The author also has discussed an analytics implementation strategy and various implementation challenges in the clinical research environment. The proposed model provided a framework to generalize, transform, and apply analytics insights to improve business and operational excellence.

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Myths and Realities of PLACEBO RESPONSE:

A 21st Century Prescription

Randomized, placebo-controlled clinical trials are the most challenging and complex aspect of development and commercialization of new drugs. The costs of conducting trials have continued to increase, trending ever upward.[1]

A dispassionate observer might question how much added value is generated from the enormous investment involved in clinical studies. Is drug development becoming more successful as a result of increased spending? Have novel (if costly) trial methods reduced the risk of extremely expensive failures?

The available evidence suggests that, despite increased costs, success rates have not improved over time.[2] A number of significant advances in technology and structural changes in research infrastructure have been developed in recent decades.[3] Coupled with legislative changes intended to foster innovation in drug development, one might anticipate shorter, more efficient studies with significantly better yields. The analogy for the ongoing trend, however, is more akin to the Red Queen's dilemma in *Alice Through the Looking Glass:* "it takes all the running you can do, to keep in the same place."[4]

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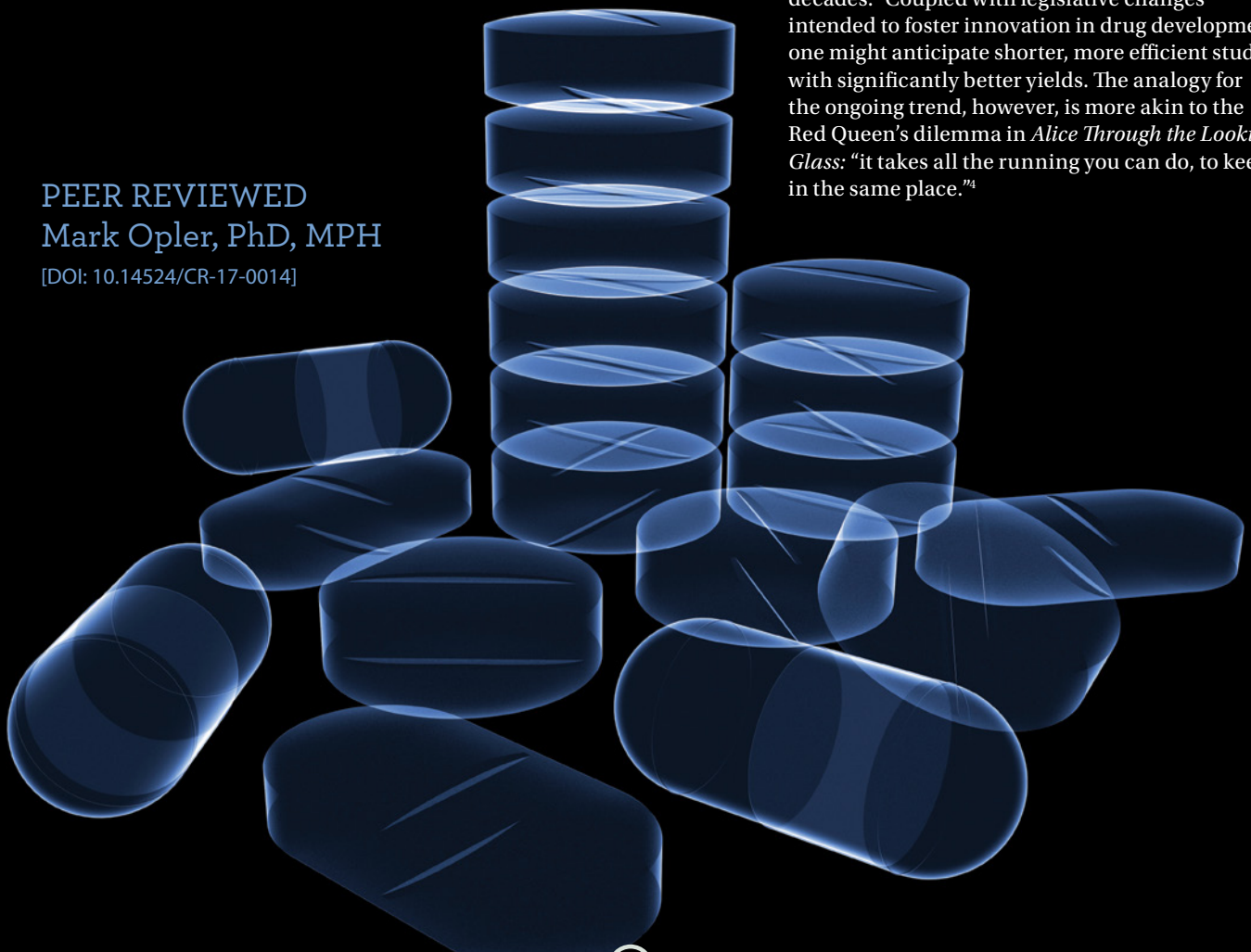

How is it possible that, following on the heels of the genomics revolution and coupled with seemingly continuous advances in biotechnology and information technology, we are spending more than ever, but are no more likely to produce positive results today than in decades prior? The reasons are difficult to reduce to a single cause, but a close examination of the matter suggests that some aspect of *quality* rather than *quantity* deserves our attention.

In other words, the pace and scope at which studies are conducted have increased, the resources expended have increased, the specialization of the work has increased, the technologies employed have increased in both number and sophistication, but perhaps the quality of data has not improved. In fact, some meaningful indicators suggest overall data quality has decreased[5,6] while the competition for clinical trials is increasing at the country level.[7]

One important indicator of clinical research quality is the extent to which trials detect effect signals (i.e., do trials separate experimental treatments from placebo). Rates of placebo response across multiple therapeutic areas are now historically high and progressively increasing.[8] Multiple reviews in different therapeutic areas, including pain,[9] epilepsy,[10] Crohn's disease,[11] dermatology, schizophrenia,[12] pediatric studies,[13] and others suggest a very distressing trend in that, year over year, the rates of placebo response are going up.

One meta-analysis shows how this affects the course of a specific development program.[14] In evaluating the efficacy of pregabalin versus placebo in peripheral neuropathy, the results indicate very clearly that the effect of placebo across different indications correlates positively with the year of study initiation. Another intriguing finding from the same meta-analysis revealed an increase in placebo response despite no attendant improvement in the efficacy of pregabalin for studies conducted after U.S. Food and Drug Administration approval.

All of this points to a population-level phenomenon in clinical research—one that is broader than an individual disorder or therapeutic area, resulting in higher placebo response across all areas of research over time.

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Reading into the Higher Response

The questions that naturally follow this realization are 1) why is this occurring? and 2) what is to be done about it? In an effort to provide practical recommendations, the following sections of this article will review three of the commonly shared (but likely false) ideas that clinical researchers have about placebo response. Some of these erroneous statements are based on direct quotes from the literature, while others are based on general attitudes encountered in practice.

MYTH #1: Placebo response is "all in your head."

Placebo response is often discussed as holding a less real or relevant status than drug response, as having no biological basis in fact, and as being limited solely to a patient's beliefs or perceptions. However, research conducted over many years suggests that there are numerous quantifiable biological reactions in response to placebo.

Beginning in the central nervous system, measurable responses in dopamine[15] and mu-opioid receptors[16]—central systems in the brain responsible for numerous critical functions—have been documented. While there is a tendency to suggest that objective physical symptoms should not respond to placebos, it is clear that the pathways mediating placebo response extend from the central nervous system to the immune system, gastrointestinal tract,[17] cardiovascular system,[18] and beyond.

Although the detailed neurobiology of placebo and associated biological mechanisms are beyond the scope of this review, the key concept is that placebo response is very real; while it may be mediated by a given patient's beliefs about medicine and the clinical experiment, the end result is anything but delusion.

MYTH #2: Placebo response is only a problem for studies using "soft" endpoints.

It may be convenient for some to believe that placebo response is only a real problem for the poor souls working in areas governed by subjectively rated endpoints, and to pity the poor investigators in depression or pain trials who are so vulnerable

Placebo response is often discussed as holding a less real or relevant status than drug response, as having no biological basis in fact, and as being limited solely to a patient's beliefs or perceptions. However, research conducted over many years suggests that there are numerous quantifiable biological reactions in response to placebo.

to study failure. However, the belief that disorders characterized by subjective symptoms are more likely to respond to placebo must be addressed by the facts at hand.

In debunking the myth that placebo response is strictly limited to patient perception, the corollary that follows is that disorders using ostensibly objective endpoints are also vulnerable to high placebo response. There should be no mistake: placebo-induced changes occur not only in mood[19] and pain,[20] but also in allergy,[21] nocturia,[22] irritable bowel syndrome,[23] cardiovascular function,[24] and many more areas. It is furthermore instructive to note that performance-based measures, including physical endurance are sensitive to the impact of placebo.[25]

MYTH #3: Placebo response is an unavoidable problem with no solution other than increasing sample size.

In the face of the evidence confronting us, it is tempting to throw one's hands up and leave it to the statisticians to tell us how much larger our studies need to be to combat this problem. The challenge with this approach is that it may contribute to a self-defeating cycle in which we chase decreased signal separation with larger studies, conducted at higher velocity, with greater operational pressure to recruit and perform. However, there are several critical models that offer a way forward, and that suggest better alignment with patient-centricity and ethical research conduct.

The Roles of Therapeutic Expectation and Misconception

How does an individual patient's level of expected improvement modify response to a placebo? Statements and actions from investigators, site staff, caregivers, and family members may significantly contribute to a patient's level of *therapeutic expectation* (defined as the level of improvement the patient anticipates in response to any treatment).

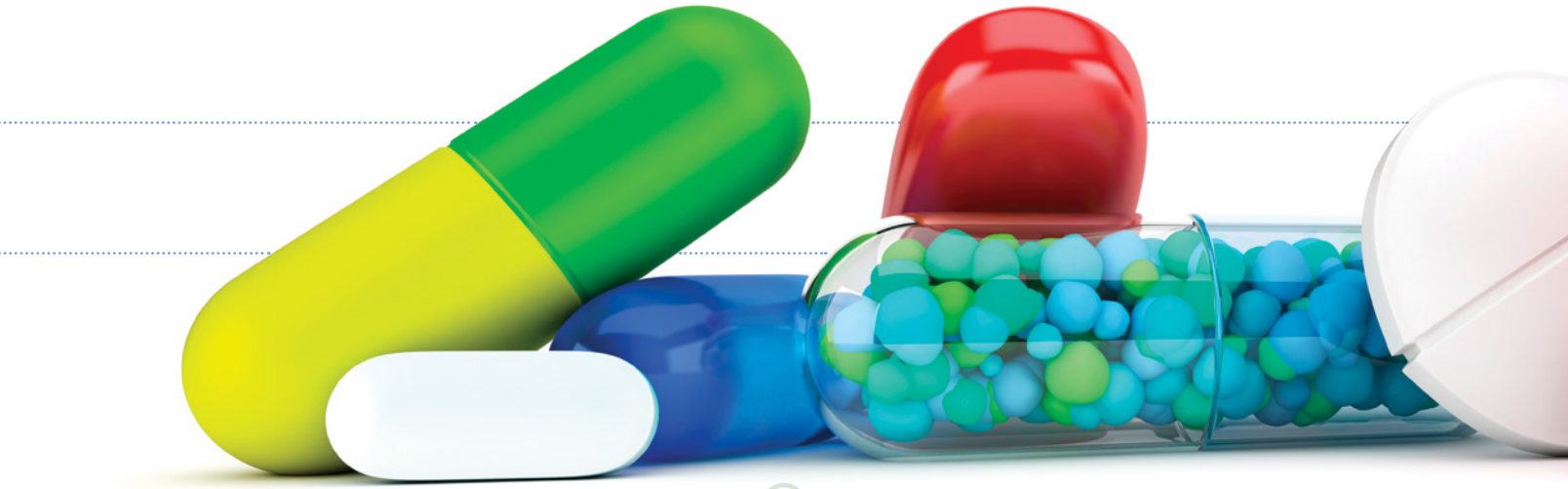
Well-intended statements from investigators trying to recruit patients (e.g., "I have high hopes for this medication" or "I believe that it will be successful") and hopeful comments from caregivers supporting patients in their deliberations about participation in trials (e.g., "You know, I read something about this drug online—it might work for you") may pave the way for increased therapeutic expectation. Placebo response mitigation strategies must incorporate investigator training, site training, and patient/caregiver training in order to be effective.

Some studies may be more prone to confounding due to therapeutic expectation than others. Pain studies are particularly susceptible to therapeutic expectation, with reported overall rates varying based on treatment modality.[26] Drugs delivered by injection, for example, may boost placebo response by increasing the patient's awareness of the treatment and by working on the belief that an injection (or other novel modality) is more effective than a standard pill.[27]

One meta-analysis[28] describes significantly higher response rates for sham (placebo) acupuncture and surgeries (approximately 40% and 60%, respectively) as compared to oral medications. The results suggest that the more novel and physically engaging a modality, the higher the likely rates of placebo response among subjects. This constitutes a challenge for the coming wave of patch, injectable, insertable, app-associated, and medication/device combinations that increase awareness of, and belief in, a treatment's effectiveness.

Patch formulations of medications may be plagued by high placebo response. Transdermal formulations of many promising treatments have been derailed due to failure to separate therapeutic response from placebo response. Treatment conditioning and expectancy effects due to cues, the use of a transdermal formulation, and other factors may elicit effects at the level of the spinal cord.[29]

A related, but distinct, issue that methodologists must tackle beyond therapeutic expectation is that of *therapeutic misconception*. Therapeutic misconception is best characterized as "a research subject fail(ing) to appreciate the distinction



between the imperatives of clinical research and of ordinary treatment."[30]

In brief, a research subject who cannot differentiate between participation in a clinical trial and receiving clinical care is experiencing therapeutic misconception. This is not necessarily due to a failure on the part of the investigator, the subject, or the informed consent process; quite simply, it is the natural tendency of people to make decisions based on individual beliefs and experience.

Reducing Therapeutic Expectation and Misconception

There are several steps that can be taken at the patient level to ensure valid, reliable data collection, and to improve the likelihood of trial success. First, investigators should work hard to ensure that all potential study subjects consistently meet several standards:

- First, that the patient *understands his/her role as a subject in a placebo-controlled protocol* (as compared to a patient receiving routine medical care) involves accurately reporting on pain and/or other symptoms as experienced during and between study visits;
- Next, that each patient *has the ability to be a good informant*—including adequate capacity and mental status—as well as appropriate motivations to participate in a research protocol; and
- Finally, that the patient *has a sufficient understanding* of the construct under investigation in order to provide a valid assessment of frequency and severity of treatment-related experiences, focusing on relevant phenomena.

Standardizing the Education Process

Operationalizing this effort may require a standardized procedure at the site level. One proposed process for communicating with patients presenting for screening is called "Patient and Rater Education of Expectation for Clinical Trials."[31] Quite simply, this takes the form of a standardized script to help investigators and site staff model the discussion that needs to take place to do the following:

- Identify patient perceptions and attitudes that might interfere with unbiased participation
- Clearly describe the purpose of the trial
- Differentiate research participation practice from medical care
- Help patients make cognitively informed decisions about the role of placebo in the trial and their role as key members of the investigative team

Most sites and investigators likely have some form of this process, standardized or otherwise, that takes place. The issue this specific process identifies and addresses is the need to counteract site staff behaviors that may influence patients toward high placebo response. It targets not only the patient directly, but all members of site staff who interact with the patient in the trial.

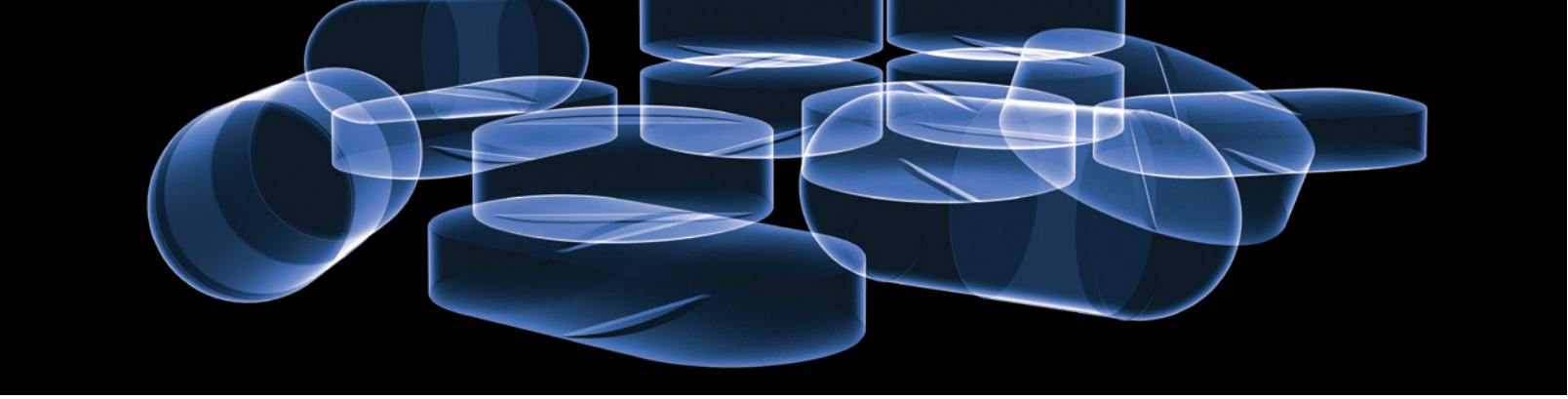
Given the frequency of therapeutic misconception that may occur (in one sample, as high as 31% of subjects expressed unrealistic beliefs about a trial in which they were participating[32]), all trial team members and their studies are likely to benefit from a more rigorous approach to this issue.

Conclusion

Improving outcomes in clinical trials and reducing the trend toward high placebo response across different therapeutic areas requires the involvement of multiple stakeholders. As stated initially, the randomized, placebo-controlled clinical trial is the pivotal event in drug discovery; it often represents the culmination of lengthy preclinical investigation, immense investment of labor, intellectual capital, and considerable financial resources.

The other critical aspects that must not be neglected are the ethical and moral imperatives tied to ensuring that all participants are fully informed—not simply procedurally, but emotionally, intellectually, and cognitively. Reducing placebo response may serve multiple critical ends, fulfilling not only the scientific and economic promise of drug development, but also enhancing our humanitarian mission in numerous ways.

Statements and actions from clinical trial site staff or from caregivers and family members may significantly contribute to a patient's level of therapeutic expectation, or the level of improvement the patient anticipates in response to any treatment.



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Applying ISO 9001 to the IRB Process

PEER REVIEWED | David Borasky, MPH, CIP | Heather Kim, MS, RAC, CIP

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An institutional review board (IRB) is an independent body that reviews proposed human subjects research in order to ensure that proposed activities are in compliance with applicable regulations and the ethical principles described in the Belmont Report. The use of the term "institutional" in IRB is derived from the reality that most clinical research studies historically were single-site studies conducted at academic medical centers, and so the IRB was viewed as a committee within the institution. However, as research evolved in the late 20th century, the model for clinical trials shifted to multicenter studies implemented at a mix of academic and non-academic research sites, with IRB oversight provided by independent IRBs that were contracted to provide the regulatory and ethical oversight in a centralized manner.

In this paper, we describe how one independent IRB utilized a non-traditional quality standard to drive improvement in IRB processes, the challenges to achieving certification, and the benefits to the organization.

BACKGROUND

Copernicus Group Independent Review Board (CGIRB) was established in 1996 to provide IRB review services to the clinical trials industry, and quickly recognized the need for a formal quality assurance (QA) program. While such programs are not required by regulation, it is an expectation of industry sponsors that providers of IRB services have a dedicated QA function. Further, a QA program should serve as an effective means for reducing organizational risk.

Organizations that provide IRB services have limited means for obtaining independent verification of the quality of their services. The industry standard for documenting the quality of independent IRBs is through accreditation by

the Association for the Accreditation of Human Research Protection Programs (AAHRPP),[1] which was founded in 2001 following a series of high-profile suspensions of research at academic medical centers. Accreditation by AAHRPP indicates that IRBs have demonstrated compliance with the organization's standards for quality and human subjects protection; however, there is no regulatory requirement that IRBs be accredited, and regulators do not consider accreditation status when inspecting IRBs.

CGIRB first received AAHRPP accreditation in 2004, and has maintained its accreditation status since then. However, the organization's leadership wanted to identify a means for demonstrating commitment to operational quality that went beyond the AAHRPP framework, and that would be recognizable by those companies in the areas of drug and medical device development. It was determined by the leadership that the organization would seek certification to the International Organization for Standardization (ISO) standard ISO 9001:2008 – Quality Management.

ISO standards promote the creation of products and services that are safe, reliable, and of high quality through the establishment and maintenance of a quality management system.

IN SEARCH OF ISO SUCCESS

ISO is an independent, non-governmental organization with global representation that publishes standards covering a broad spectrum of industries, including agriculture, manufactured products, technology, and healthcare. ISO standards promote the creation of products and services that are safe, reliable, and of high quality through the establishment and maintenance of a quality management system (QMS).[2] The standards are utilized widely in the drug and medical device industry to help increase productivity while minimizing errors and waste by focusing on domains covering the QMS; management responsibility and resource management; product realization; and measurement, analysis, and improvement.

Although our organization was not aware of any other IRBs that had achieved ISO certification, the leadership believed that ISO would be a recognizable certification that clients would accept as an independent measure of organizational quality. ISO was also viewed as an optimal fit because of its focus on customer service.

Compliance with the ISO standards requires a commitment of resources as well as a commitment by organizational leadership. Top management is responsible for the system's effectiveness, and makes sure stakeholders throughout the organization understand how they contribute to the QMS.

The process of obtaining certification began with a year-long self-study of internal processes. CGIRB engaged with North Carolina State University's Industry Expansion Solutions program to facilitate this process. Preparatory activities included supplementing existing organizational policies and procedures, and the development of ISO-specific standard operating procedures (SOPs).

In addition to revising written policies, management worked to identify the processes that would be considered within the scope of the certification. The process concluded with a certification assessment in which CGIRB's revised policies and procedures were reviewed and all process areas that were in scope were audited. Full certification to the ISO 9001:2008 standard was achieved in 2010.

Organizations must be prepared to allocate sufficient financial and human resources to the certification effort. The allocation of resources begins with preparing for certification, which can take up to a year, and continues through the time when certification is achieved and into the ongoing maintenance phase.

TALLYING THE BENEFITS

The ISO standards provided a strong framework to improve existing processes, and the organization experienced quantifiable benefits across the company with the adoption of ISO 9001, in part because it established a mindset and provided a methodology for tracking operational metrics in every department.

One of the simplest actions that had significant effects was implementation of measurement tools for metrics such as turnaround time, error rates, and client feedback. These measurement tools introduced a new level of accountability that helped to increase awareness of business goals with both staff and managers, and helped to monitor possible problematic patterns.

Prior to certification, the organization had informal goals for processing submissions, such as processing new principal investigator submissions within 24 hours; however, the turnaround times had not been tracked. The organization began systematically tracking the turnaround times for processing various submission types, and those numbers are used as a reliable metric to support communications on expected delivery timelines to clients. When turnaround times increase unexpectedly, it is recognized quickly and serves as a trigger for management to analyze the workflow and determine what kind of issues might be contributing to the deviation. The continuous monitoring means that problems can be identified sooner and additional resources or re-training can be instigated to address potential problems quickly.

The QMS is also monitored through routine internal auditing. Although the organization is subject to frequent external audits by clients and the British Standards Institution, which audits CGIRB for its ISO 9001 certification, systematic internal audits are still required by the ISO standards. Internal audits are a way to make the company self-monitor and provide the business with opportunities to detect and address non-conformities, and to pre-empt findings from external auditors, which again translates to higher confidence in the organization's services.

Internal process audits are conducted on the key functional areas within the company by organizational staff who are trained as auditors. The organization values the internal audit process for providing a systematic review of key processes to check that employees are following the company's SOPs, as well as customer expectations and regulatory requirements. Following SOPs ensures consistent products and services, which translates to the company's reliability. Internal audits not only identify issues with conformance to the processes, but also opportunities for improvement that are shared with process owners and organizational leadership.

Clients from the industry recognize the standard, and understand what organizations must do to obtain and maintain certification. Clients know that the certification requires a commitment to quality, an active risk-mitigation approach to management, and a focus on customer service.

THE SENSIBILITY OF STANDARDIZATION

ISO's requirements for the standardization of processes have also benefited the organization by contributing to a reduction in internal errors—those made by the organization that clients identify and result in documents being corrected and regenerated. Internal errors exclude client-generated errors and any errors identified during the internal quality check process before documents are transmitted to clients.

A comparison of 2010 versus 2016 data shows a remarkable 90% decrease in the overall internal error rate. The organization continues to be committed to reducing errors, and tracks errors at a more granular level by submission-type, which helps to focus on key performance metrics and to implement process improvements on a continuous basis.

Standardization of processes and commitment to reducing errors have also contributed to a reduction in turnaround time; 2010 versus 2016 data show that there has been a 48% improvement in processing new protocol submissions. New investigator submission turnaround times also improved by 7%, and with an aggressive 24-hour

turnaround time goal, that is a significant accomplishment. Thus, ISO has led to a more effective use of human resources to complete work processes without compromising the quality of the product or the timeliness of delivery.

The benefits of ISO affect CGIRB's employees, as well. CGIRB created standardized job guides for processes, which are used to audit against in internal audits. Ensuring that SOPs and job guides are followed also ensures that they are up to date if there have been any changes in procedures.

Accurate and complete job guides have a positive impact on employee training and onboarding. Further, the job guides and SOPs can be used as reliable references for new staff, which helps in facilitating the transition to becoming proficient team members. CGIRB has clear company quality objectives and goals, which are communicated to all staff so they know what is expected of them.

THE CHALLENGES OF CERTIFICATION

There are challenges associated with obtaining ISO certification, beginning with a commitment on the part of the organizational leadership. Organizations must be prepared to allocate sufficient financial and human resources to the certification effort. The allocation of resources begins with preparing for certification, which can take up to a year, and continues through the time when certification is achieved and into the ongoing maintenance phase.

Organizations may need to establish or expand QA departments and establish a cadre of staff who can conduct internal audits. Key performance indicators and other metrics have to be identified and systems have to be established to collect and analyze data for use in improving performance.

In addition to internal audits, an organization must commit to one or more surveillance audits per year by its certifying body, and a complete recertification every three years. Additional requirements include establishing robust processes for managing corrective and preventive actions, and identifying and qualifying business critical vendors on a systematic basis.

2010 versus 2016 data shows

90%

decrease in the overall internal error rate

48%

improvement in processing new protocol submissions

Another practical challenge is derived from CGIRB's status as an outlier among certified organizations. Auditors from the certifying organization are typically unfamiliar with IRBs, and there is a learning curve for them when assessing an IRB for the first time. IRBs seeking certification must exercise patience during surveillance assessments, until the assessor builds up familiarity with the organization and what it does.

CONCLUSION

Adoption of the ISO 9001:2008 – Quality Management standard led to a measurable improvement in the quality of the product and more effective use of our human resources. The application of the standard to the processes followed by an IRB require an investment of human and financial resources and a commitment on the part of organizational leadership. However, we conclude that the return on investment justifies the costs.

The ISO standards provide a framework for implementing a QMS that goes beyond the basic regulatory requirements and contributes to an IRB's mission of protecting participants in clinical research. The standards ensure that the organization remains focused on continuous process improvement that is data-driven, while maintaining high standards of customer service and accountability.

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JUNE 2017 CLINICAL RESEARCHER
HOME STUDY

APPLYING QUALITY IMPROVEMENT TO CLINICAL TRIALS

Integrated Clinical Analytics Model to Improve Business and Operational Excellence in Clinical Research

LEARNING OBJECTIVE
After reading this article, participants will be able to differentiate between various types of data analytics and explain how they will help organizations to improve business and operational excellence in clinical research.

DISCLOSURE
Kaali Dass, PMP, PhD: *Nothing to disclose*

1. Which of the following is NOT mentioned as a shortcoming of legacy applications used by contract research organizations to address the unique needs of their customers?

A. They lack integration.
B. They could never be justified on a cost basis.
C. They lack access to a single source of truth.
D. They do not provide actionable information.

2. What does MIOT stands for?

A. Medical Internet of Things
B. Mobile Internet of Things
C. Multiple Interconnected Operational Technology
D. Mobile Interconnected Operational Technology

3. According to the article, which of the following is a key benefit of real-time data capture and validation?

A. It can be used to build a data warehouse to analyze data about competitors' products.
B. It can help start-up organizations use historic analytics to improve clinical trial success.
C. It allows users to check data quality only when pre-specified milestones are reached.
D. It can reduce manual data entry errors and improve overall data quality and accuracy.

4. The article points out which of the following sets of challenges to conducting clinical trials?

A. Difficulties managing staff from many cultures and paperwork from geographically distributed sites.
B. Pressures from the high cost of research and numerous rules and regulations.
C. Failure to analyze issues properly because enough data can never be collected on time.
D. The same processes and procedures cannot be applied to different trials because the investigational products are too different.

5. According to the article, how do analytics help the clinical research industry?

A. By aiding decision-making mainly about new equipment purchases and hiring needs.
B. By reducing costs closely associated with site selection and study start-up.
C. By providing unique insights, generating new knowledge, and improving outcomes.
D. By allowing research teams to consider a broader array of study opportunities outside their traditional areas of focus.

6. What are the functional areas of data architecture highlighted in the article?

A. Foundational, Transactional, Operational Analytics, Clinical Analytics/Study Reporting, Business Analytics
B. High-Volatility Data, Medium-Volatility Data, Low-Volatility Data, End-to-End Data Transparency, Business-to-Business Data Sharing
C. Real-time Analytics, Batch Analytics, On-Demand Analytics, Prespecified Endpoint Analytics, Cyclical Analytics
D. Site-Reported Analytics, Patient-Reported Analytics, Lab-Reported Analytics, Monitor-Reported Analytics, Investigator-Reported Analytics

7. What are the different types of data analytics highlighted in the article?

A. Structured, Unstructured, Anonymized, Disaggregated, Randomized
B. Real-time, Batch, On-Demand, Prespecified, Cyclical
C. Transactional, Operational, Clinical, Business, Predictive
D. Predictive, Prescriptive, Preventive, Prescreened, Preoperative

8. What is the advantage of integrated clinical analytics model (ICAM)?

A. It provides a framework to measure, analyze, and improve study outcomes.
B. It allows for better study budget forecasting and enrollment management.
C. It promises better investigational product management and safety monitoring.
D. It provides tools for retrospective analysis of statistical biases due to placebo effect.

9. According to the article, what are the areas of implementation challenges of ICAM?

A. Culture, Training and Development, Payroll, Change Management, Governance, Regulation, Transparency
B. Data, Privacy, Security, Validation, Governance, Training and Development, Outcome
C. Security, Validation, Employee Satisfaction, Tenure and Promotion, Training and Development, Regulation, Quality Assurance
D. Data, Privacy, Security, Quality Control, Risk-Based Monitoring, Standard Operating Procedures, Transparency

10. According to the conclusion, how does clinical research benefit from analytics?

A. Through increased productivity and performance from improved budgeting and staffing.
B. Through improved decision-making and insights on business and operational excellence.

C. Through cost reductions and improved customer experience at the site and sponsor levels.
D. Through improved data security and data governance based on regulatory authority feedback.

Myths and Realities of Placebo Response: A 21st Century Prescription

LEARNING OBJECTIVE
After reading this article, participants will be able to outline the challenges posed by placebo response in the context of clinical trials and to discuss different methods for alleviating those challenges.

DISCLOSURE
Mark Opler, PhD, MPH: *Employee of ProPhase, LLC*

11. "Placebo response" refers to which of the following?
    A. Assent to use of placebo is included in informed consent forms for controlled studies.
    B. The reduction or remission of symptoms in subjects receiving placebo in clinical trials.
    C. Adverse reactions after withdrawal of experimental treatments in placebo-controlled trials.
    D. The failure of research subjects to understand the use of placebo in clinical trials.

12. Over time, placebo response has followed which of the following trends?
    A. Increasing only in studies of subjective endpoints, such as pain.
    B. Decreasing in most indications where it has been studied.
    C. Increasing in almost every indication where it has been studied.
    D. Decreasing only in studies conducted outside the United States.

13. Patients in placebo arms of clinical trials can be said to do which of the following?
    A. Fail to show responses in "hard endpoints" such as blood pressure.
    B. Always fully understand their role as research subjects.
    C. Cannot have adverse reactions as they are not on drug.
    D. May show clinically meaningful changes in both objective and subjective endpoints.

14. Which of the following is true of performance-based measures, such as physical endurance?
    A. They are not useful in proving the endpoints of clinical trials.
    B. They show no evidence of change in patients receiving placebo in clinical trials.
    C. They are sensitive to the impact of placebo in patients receiving it.
    D. They are not vulnerable to placebo response as they can be objectively measured.

15. "Therapeutic expectation" is defined as which of the following?
    A. The level of improvement a research subject expects to experience.
    B. Another way of measuring treatment effect size in depression studies.
    C. The difference between placebo improvement and drug improvement.
    D. The likelihood of receiving placebo in a multi-arm trial.

16. Reductions in placebo response may occur due to which of the following?
    A. Investigator statements such as "we have high hopes for this medication."
    B. Supportive remarks from site staff.
    C. News reports about an innovative new experimental treatment.

D. Better patient education about the use of placebo.

17. "Therapeutic misconception" is defined as which of the following?
    A. The failure of research subjects to differentiate between research and medical care.
    B. A phenomenon caused by incorrectly documented informed consent.
    C. Miscommunication between research team members that is not a problem for most clinical trials.
    D. The failure of experimental drugs to reach therapeutic targets when administered incorrectly.

18. Which of the following about a treatment is NOT mentioned as likely to lead to a higher placebo response?
    A. The treatment modality is perceived as a more novel one.
    B. The treatment is delivered in a more physically engaging manner.
    C. The treatment is delivered in a patch formulation.
    D. The treatment is delivered only by non-physician study coordinators.

19. Investigators can help mitigate placebo response if they do which of the following?
    A. Provide subjects with additional supportive guidance throughout the trial.
    B. Limit discussion of the purpose of the trial.
    C. Differentiate research participation from medical care.
    D. Remind patients that all treatment will be individually tailored to their needs.

20. Improving outcomes in clinical trials and reducing the trend toward high placebo response across different therapeutic areas does NOT do which of the following?
    A. Require the involvement of multiple stakeholders.
    B. Serve an ethical as well as a methodological purpose.
    C. Improve the likelihood of trial success.
    D. Impact the study startup timeline.

Applying ISO 9001 to the IRB Process

LEARNING OBJECTIVE
After reading this article, participant will be able to describe the challenges associated with applying the ISO 9001:2008 standards for quality management in the institutional review board environment.

DISCLOSURES
David Borasky, MPH, CIP; Heather Kim, MS, RAC, CIP: *Employee of Copernicus Group IRB*

21. Which of the following is the industry standard for documenting the quality of institutional review boards (IRBs)?
    A. Certification under the International Organization for Standardization (ISO) 9001.
    B. Registration with the U.S. Food and Drug Administration (FDA).
    C. Accreditation from the Association for the Accreditation of Human Research Protection Programs.
    D. Establishment and publication of effective standard operating procedures (SOPs).

22. IRBs were placed under increased scrutiny for which of the following reasons?
    A. The Tuskegee syphilis study.
    B. Suspensions of high-profile academic medical center IRBs.
    C. The publication of the "Common Rule" IRB regulations in 1991.
    D. The deaths of study subjects in gene therapy research.

23. The ISO can be described as which of the following?
    A. An independent, non-governmental organization that publishes quality standards.
    B. An independent organization that accredits IRBs internationally.
    C. The FDA's quality division for the regulatory oversight of IRBs.
    D. An organization that publishes standards to be followed by clinical study sites.

24. Under ISO, which of the following is responsible for the quality system's effectiveness?
    A. The head of the Quality Assurance unit
    B. The chairperson of the IRB
    C. The organization's CEO
    D. Top management

25. According to the article, the implementation of which of the following can have a significant positive effect on quality?
    A. Measurement tools for metrics
    B. Process controls expected by sponsors
    C. SOPs copied from other organizations
    D. Annual process audits by the FDA

26. ISO certification requires ongoing monitoring through which of the following?
    A. Documentation in IRB records
    B. Quality stakeholder meetings
    C. Systematic internal audits
    D. Systematic independent audits

27. Internal process audits provide a systematic review of key processes to check that employees do which of the following?
    1. Recruit family members into trials
    2. Follow organizational SOPs
    3. Meet regulatory requirements
    4. Meet customer expectations

    A. 1, 2, and 3 only
    B. 1, 2, and 4 only
    C. 1, 3, and 4 only
    D. 2, 3, and 4 only

28. Internal errors are described in the article as which of the following?
    A. Those made by the organization that clients identify and that result in corrections being made.
    B. Those generated by clients that are identified by IRB staff and corrected.

C. Those identified during internal quality control processes before documents are sent to clients.
D. Those whose causes remain known only to top management in the organization.

29. Companies may benefit from having standardized job guides because of which of the following?
    A. Accurate and complete job guides facilitate employee training and onboarding.
    B. Accurate and complete job guides guarantee faster turnaround times.
    C. They communicate company quality objectives and goals to staff.
    D. They implement measurement tools for metrics.

30. Challenges of obtaining ISO certification include which of the following?
    1. Investment of financial and human resources.
    2. Commitment to recurring surveillance audits by the certifying body.
    3. Approval from national and international regulatory authorities.
    4. Initial identification of key performance indicators and establishment of systems to collect and analyze the data.

    A. 1, 2, and 3 only
    B. 1, 2, and 4 only
    C. 1, 3, and 4 only
    D. 2, 3, and 4 only