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WASHINGTON REPORT
Streamlined Trials for New Antimicrobials

CISCRP CORNER
The Full Story: Mapping Patients' Health Journeys

CLOSING THOUGHT
Avoiding Common Pitfalls of Market Landscaping

The Cloud Has Been Conquered, But the Dust is Still Settling

LISA HENDERSON
Editor-in-Chief

Recently, Oracle Health Sciences released survey results around clinical data management (bit.ly/2zP4B1l). Conducted by Informa Pharma Intelligence, the survey found many data challenges that have the potential to hinder the clinical trials process. Results showed that 81% of respondents cited data governance issues as the biggest challenge in meeting regulatory compliance, which include duplicate data/inconsistent data, data quality, and data integrity/traceability.

One of the major challenges noted not only by respondents in this survey, but by attendees to the recent Veeva Systems R&D Summit, is the increased number of data sources. The Oracle/Informa survey asked, "How many different data sources do you have for a typical clinical trial," with the following results: 50% of respondents said between 1-5, 37% said between 6-10, and 13% said 11 or more.

At Veeva Systems' Reinventing Clinical Data Management media roundtable, Henry Levy, chief strategy officer for Veeva, gave the group a brief history of clinical data. "Thirty years ago, electronic data wasn't common and all of your data was in one place, and it was ugly, but it was centralized and managed in one place. And then EDC was a revolution, with companies like Oracle and Medidata coming in, which was a massive improvement—and that was a really good thing. But it actually broke everything else, because now you had a clinical data management system (CDMS) that was supposed to clean your data, and then you had an EDC system that was doing a part of the data, which at the time, 70%-75% of your data was EDC data."

But now, as the survey points to, and Levy highlighted, clinical data sources have morphed to where EDC comprises only 20%–30% of data, and along with ePRO, mHealth, lab data, and more…leaving CDMS trying to catch up. Shelley Padgett, senior director of IT at Eli Lilly & Co., shared her own experience. "I was in clinical development, and I left for commercial for 10 years and when I came back and saw the number of third-party organizations involved, the amount of data and platforms, was exploding. So we've been in a model to bring that together so that our workflows can come together, but with a smaller set of platforms."

The Oracle survey respondents answered this question, "What is your biggest challenge when it comes to meeting regulatory compliance with your clinical trial data?" Data quality response was 30%, duplicate data/inconsistent data was 26%, and data lineage/traceability was 25%.

For Padgett, the challenge with data confidence has its roots in that data explosion. "It's hard to find any one person in a company who knows what the flow of that data looks like, and how all that works." Eli Lilly has spent a very concerted effort documenting the flow of data, which she said is complicated. "You could be on this EDC system, this version of this EDC system transferring to this version of that, transferring to that version…" But for Padgett, the key is in simplification.

To view the free on-demand Webcast around Oracle's survey results, please visit bit.ly/2ICgVV8.

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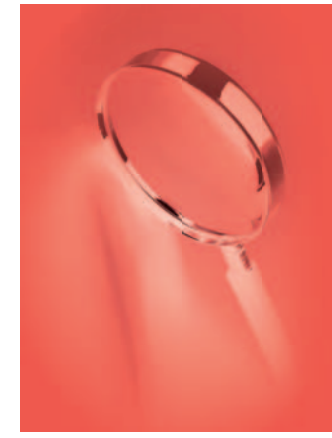

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NEWS AND ANALYSIS

COMMENTARY

WASHINGTON REPORT

FDA SUPPORTS STREAMLINED TRIALS FOR NEW ANTIMICROBIALS

The critical need for new medicines to combat infectious diseases is prompting FDA to join with other federal health agencies and the biomedical research community to advance the science, regulatory policies, and reimbursement strategies to promote innovation in this area. A main strategy is to design research programs for antimicrobials intended for limited use by patient populations exposed to lethal pathogens. The development and approval of new antibiotics traditionally involves large confirmatory clinical trials that are long and costly, but appropriate for therapies that are widely used and can generate a sufficient return on investment to sponsors. To remain effective against lethal pathogens, however, new antimicrobials need to be prescribed very sparingly, cutting revenues in the process. Hence, a different research model is needed to limit research costs while overcoming obstacles in identifying and enrolling sufficient numbers of patients with target pathogens.

These challenges have curbed industry investment in developing new antimicrobials. The Pew Charitable Trusts reports that as of June 2018 only 42 new antibiotics were in clinical development to treat serious bacterial infections (see bit.ly/2O1fiFF). Just one in five, moreover, are likely to succeed, and only a handful have potential to address serious resistance problems, such as gram-negative bacteria, which cause particularly hard-to-treat infections.

To address this crisis, FDA Commissioner Scott Gottlieb recently unveiled a 2019 Strategic Approach for Combatting AMR (antimicrobial resistance) at a meeting Sept. 14 organized by Pew (see bit.ly/2xCQTfz). The plan includes policies and programs to encourage development of new drugs, diagnostic tests, and vaccines; to promote responsible stewardship of antimicrobials in animals and humans; to improve surveillance of antimicrobial use and resistance; and to advance research for developing new tools, standards, and policies in this area. Gottlieb noted that FDA expects that preclinical and clinical programs for certain new infectious disease therapies will follow streamlined approaches to clinical development, including smaller, shorter, or fewer clinical trials.

FDA previously outlined such an approach in issuing draft guidance in June to help manufacturers utilize the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) in developing new therapies (see: bit.ly/2OF3IgF). The LPAD program was authorized by the 21st Century Cures Act, but has been challenging for both sponsors and FDA to implement. The guidance describes how sponsors may seek approval of qualifying products that treat small numbers of seriously ill patients based on data from streamlined research programs.

New reimbursement strategies also are needed to support the development of products that would be prescribed and used on a highly limited basis. To maintain a robust pipeline for antibiotics, Gottlieb recognized at the Pew meeting the need to "change the perception that the costs and risks of antibiotic innovation are too high relative to their expected gains."

FDA is exploring a subscription-based model that charges hospitals a flat rate or licensing fee for access to a certain number of doses each year of a new antimicrobial. Other innovative reimbursement strategies could involve milestone or add-on payments for new technology. By creating a predictable revenue stream, this kind of "pull incentive," Gottlieb explained, would "create natural markets for drugs targeted to rare but dangerous, multi-drug resistant pathogens that can threaten human health.

To advance regulatory science in this area, the Office of Antimicrobial Products in the Center for Drug Evaluation and Research (CDER) has requested input from stakeholders on developing an annual list of science initiatives likely to spur development of new antimicrobial products.

In addition, the Center for Biologics Evaluation and Research (CBER) is supporting development of non-traditional alternatives to small molecule drugs, including bacteriophages, live biotherapeutics, and fecal microbiota for transplant. CBER also is exploring vaccines to prevent infections caused by microbes resistant to current treatment, which ideally would reduce the risk of infections that require treatment with new antimicrobials. Equally important at FDA is support for developing new *in vitro* diagnostics able to detect disease rapidly, identify appropriate treatment, and track resistance.

— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

9/28/18: Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics Guidance for Industry.

9/24/18: Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications

9/20/18: Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank (draft)

8/23/18: Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials for Drug Product Development Guidance for Industry (draft)

8/6/18: Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment Guidance for Industry (draft)

EU REPORT

THE EUROPEAN UNION GUESSING GAME

The workings of the European Union are notoriously complicated, with the result that misunderstanding is commonplace, even among those who might like to know more about it (to say nothing of those who should know more—as an upcoming debate about digital health will reveal).

The byzantine relations between the EU's institutions and the Jesuitical distinctions in its terminology are aptly illustrated by the fact that the European Council is quite different from the EU Council of Ministers, and the President of the Council is not the same as the rotating Presidency—and none of those are to be confused with the Council of Europe, which is a different animal altogether with nothing to do with the EU. Similar nuances between the rights and powers of the EU and its member states, and between concepts such as the single market, the customs union, and border controls, are currently bedeviling the EU's own discussions on issues as diverse as migration policy, the rule of law or—most conspicuously—Brexit.

In the highly specific field of health, there are inevitable confusions because of the curious arrangements in which the EU has some responsibility for public health while the individual countries are in charge of their own healthcare. But that halfway-house is not the focus here.

What provokes this reflection is a report that was discussed last month in the European Economic and Social Committee on "Digital Transformation in Health and Care." The EESC is one of the EU's institutions, boasting 350 members, who have an advisory role in EU affairs. In dealing with the "Impact of digital transformation on social and health systems," the draft report says it supports "the four-pillar process for cross-border joint work on digital transformation in health and care."

But in reality it doesn't support any such thing. Because that process simply doesn't exist. What the report then lists—over the course of an entire page—is the EU plan for developing a system for closer coordination of national health technology assessment (HTA) arrangements. There is only one common point: HTA and digital health both concern health. But in other respects, they are utterly different.

Many readers of *Applied Clinical Trials* are familiar with the EU draft regulation on HTA, and would recognize the account—incongruously situated in this report supposedly on digital health—of legislative proposals for a European coordination group of experts from national HTA bodies, and the four key elements of joint clinical assessments, joint scientific consultations, cooperation on horizon scanning, and voluntary cooperation among member states on assessments for products not covered by the new law. But they would be understandably and justifiably surprised to see them listed in this EESC report on the EU's digital health strategy.

Just for the record, there is an EU network on eHealth. It was created in 2012 to advance interoperability, as a result of the EU directive on patients' rights in cross-border healthcare. This connects national authorities responsible for eHealth, and offers advice on interoperability and standardization in line with a 2018-2021 work plan, and it has recently held its 13th meeting. And since 2004, two EU "Action Plans" on eHealth have been agreed, along with the creation of an eHealth Stakeholders Group. But none of them have anything to do with HTA.

There is also a joint EU project to provide the eHealth network with technical and scientific advice, which focuses on setting up a digital service infrastructure for eHealth. There is an eHealth stakeholder group, which includes European umbrella organizations in research, industry, standardization and associations representing patients, professionals, and hospitals. And also just for the record, the Commission is planning to review the role of the eHealth network so as to improve the interoperability of patient data and access by the citizen. It also intends to move ahead with technical specifications for a European electronic health record (EHR) exchange format,.

But you won't read any of this in the EESC report on the subject. Instead it will tell you all about HTA. They mixed up two completely different and unrelated EU health policy initiatives. And this despite four months work in a specially-constituted "Study Group on Digital Transformation/Health and Care," with six members and three experts.

So if they can't get it right—and that is their sole job—then who can be blamed for occasionally mixing up the European Council with the Council of Europe?

— Peter O'Donnell

EMA NOTES

EMA EDUCATES ON BIOSIMILARS

The European Medicines Agency (EMA) and the European Commission have published additional information material on biosimilar medicines, as part of their ongoing collaboration to improve understanding of biosimilars across the EU.

The new material includes an animated video for patients that explains key facts on biosimilar medicines and how EMA works to ensure that they are as safe and effective as their reference biological medicines. View the video here: bit.ly/2N6Grmn

RARE DISEASE DEVELOPMENTS

In 2000, the EU's orphan designation program was launched to encourage companies to research and develop medicines for rare diseases. By the end of 2017, over 1,900 medicines had been granted orphan status that gives access to specific incentives that make it more attractive for companies to develop these treatments. To date, over 140 orphan medicines are marketed in the EU providing new treatment options for patients.

CISCRP CORNER

SHARING STORIES OF CLINICAL TRIAL PARTICIPATION FROM START TO FINISH

How mapping patients' health journeys can drive a deeper understanding of their experiences and motivations

As our recent columns have shown (see bit.ly/2NPSIfR), CISCRP's 2017 Perceptions and Insights (P&I) survey—reaching 12,427 people around the world—elucidates areas of opportunity to improve clinical trials. The results show, for example, that more than half (58%) of the public reports that they would begin a search for a clinical trial by asking their doctor, yet the majority (73%) of people mention that they never or rarely discussed clinical trials as a treatment option.

Lengthy study visits (11%), travel time to the study site (23%), and the possibility of being placed in the placebo group (24%) continue to be challenges that study volunteers face when participating in a clinical trial. And when participation is over, 91% of patients feel it is important to receive a copy of their study results.

The P&I data is helpful in quantitatively providing insight into *"what"* current patient attitudes and experiences are regarding clinical trials.

CISCRP has begun conducting Patient Journey Workshops (PJWs) in a creative and intimate setting to begin answering the *"why"* and *"how"* behind the quantitative survey results. In these workshops, patients are given the opportunity to share their clinical trial journeys by visually recreating their intricate and personal stories. With this approach, patients with chronic illnesses can reveal how their experiences with available treatments might weigh into their decision to participate, as well as how the symptoms of their condition or additional socioeconomic factors might affect their experience with clinical trial participation.

Furthermore, through PJWs, patients can share why a streamlined transition back to standard of care is critical, and why receiving study results is paramount once clinical trial participation is over.

Diving beneath the surface

The PJW is framed by the clinical trial participation timeline (i.e., before participation, during participation, and after participation) to capture feedback from a group of patients in a chronological manner. The group of patients invited to participate can either reflect the demographics of study volunteers for a potential clinical trial, or represent a diverse group of patients with a mix of conditions and experiences, and offer insight into unique needs and preferences of a patient population along a clinical trial timeline.

During the first part of the workshop, participants are asked to share their past experiences with clinical trials. Questions regarding which communication channels are most relevant, where patients learn about clinical trials, and why they decided to participate are asked during the "before-participation" stage, to help provide insight to the nuances of the decision-making process. As implied by the P&I survey findings, the involvement and support of a healthcare provider can be very important to patients in their decision to participate in a clinical trial. The PJW approach can help uncover why patients view their doctor as a trusted resource—they may feel their doctor is most familiar with their health status and can best help determine whether a clinical trial is the optimal option for them.

At the "during-participation" stage, the workshop approach allows the participants to delve more deeply into experiences with study requirements and why they might be a hurdle for some. In past PJWs, CISCRP has learned that the severity of a condition and symptoms can impact a patient's ability to complete questionnaires (hand-written ones especially, if issues with dexterity are present in the patient), to travel back and forth from the clinic, and to fast before clinic visits. This stage of the PJW has also revealed why certain socioeconomic factors make reimbursement and compensation critical, as it may be difficult for some patients to pay for travel out-of-pocket, to take time off work, or to afford childcare.

Finally, at the "after-participation" stage, the workshop has shown that having a clear plan in place to transition back to standard of care can help patients not feel abandoned after their trial participation has ended, and that patients value receiving their study results because this can help them determine if the study drug worked for them, and see how their participation helped others.

The sharing of the patients' actual clinical trial experiences highlights the drawbacks of their participation, so that during the second part of the workshop, patients can use their past experiences to brainstorm the ideal clinical trial journey. Once the workshop is complete, the actual journey map is overlaid on the ideal journey map to identify areas of opportunity for the sponsor to consider.

The "so what?"

CISCRP's experiences conducting Patient Journey Workshops have generated valuable and actionable insights for sponsor companies. As clinical trials become increasingly more customized to individual patient needs associated with rare and highly specialized disease conditions, there is much to learn by letting patients share their unfiltered experiences (see bit.ly/2zILyWg; bit.ly/2Nf3J9o).

Patient Journey Workshops differ from other methods of soliciting patient feedback, which often are more tailored to what sponsors want to learn, leaving little room for patients to share what is most important to them. By purposefully dedicating time to listen to patient stories and ideas for how to improve clinical trials, industry stakeholders can learn the underlying reasons why certain aspects of clinical trials are more important for patients than others.

Ultimately, clinical trials will be better suited to engage each patient from start to finish.

— CISCRP Research Services: Nova Getz, Annick Anderson, Jasmine Benger

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Pharmacovigilance, just like drug development, is an iterative process where all stakeholders work proactively and collaboratively to ensure a systematic approach to safety monitoring. The industry is transitioning to more active safety surveillance activities, creating greater demands for more comprehensive and innovative approaches.

Today, artificial intelligence (AI) and machine learning are being viewed as providing potential insights for enhancing patient safety. While still early in usage, AI is demonstrating the feasibility to predict potential issues, further enhancing patient safety in clinical trials.

Register today for an informative webinar and learn how AI is transforming clinical development and enhancing patient safety:

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NEWS NOTES

M3 WAKE ACQUIRES PRI

M3 Wake Research, a clinical research subsidiary of M3 USA, the U.S. business segment of M3 Inc., a global healthcare technology, research, media, and marketing firm, acquired Pharmacology Research Institute (PRI). PRI conducts multispecialty clinical studies for domestic and international pharmaceutical companies, with a special expertise in psychiatry, neurology, and gerontology. This acquisition solidifies the position of M3 Wake Research as a significant North American research network, with PRI enhancing M3 Wake Research's expertise in neuroscience.

The addition expands the organization to provide coast-to-coast coverage in the US and incorporates communities of nearly 20 million people. M3 entered the clinical research business in the U.S. in February, via the acquisition of Wake Research, one of the largest independent Phase I-IV clinical trial site service companies in North America.

PREMIER RESEARCH EXPANDS IN ASIA-PACIFIC

Premier Research has again expanded its presence in the Asia-Pacific region to include South Korea, Singapore, and Taiwan. The moves increase activities in Australia and New Zealand, where the CRO has been conducting clinical trials for many years, and also adds to the company's presence in some of the world's fastest-growing biopharmaceutical markets.

Premier Research's enhanced footprint will strengthen the company's reach across these markets and provide greater access to patients, a major benefit to a CRO engaged in rare disease studies and other research that relies on access to hard-to-find patient populations.

— Staff and wire reports

QUALITY MANAGEMENT

SURVEY: LACK OF CONFIDENCE IN CLINICAL TRIAL DATA DELAYING DRUG DEVELOPMENT

Pharmaceutical companies share concerns over their ability to bring more drugs to market faster due to clinical data challenges. A new global study, commissioned by Oracle Health Sciences and conducted by Pharma Intelligence, revealed that 57% of the clinical researchers surveyed believe that their clinical data issues result in trial delays.

In addition to trial delays, 81% of respondents cited data governance issues as the biggest challenge in meeting regulatory compliance. The top three data issues according to survey respondents were duplicate data/inconsistent data, data quality, and data integrity/traceability.

"Data governance is our top concern because clinical data quality issues can hinder a trial's completion," said Melonie Longan, director, data operations, functional services, Premier Research, a CRO.

When asked what the top three operational challenges were with their clinical trial data, 51% cited data completeness, 45% said data quality, and 43% said data cleaning.

"The kind of clinical data quality issues such as those highlighted in this report can have significant negative impacts," said Julie Barenholtz, principal clinical data manager, Cytel Inc., a CRO. "As a data company, we are always looking for ways to improve the quality of the data and process it efficiently so that patients have access to treatments as quickly as possible."

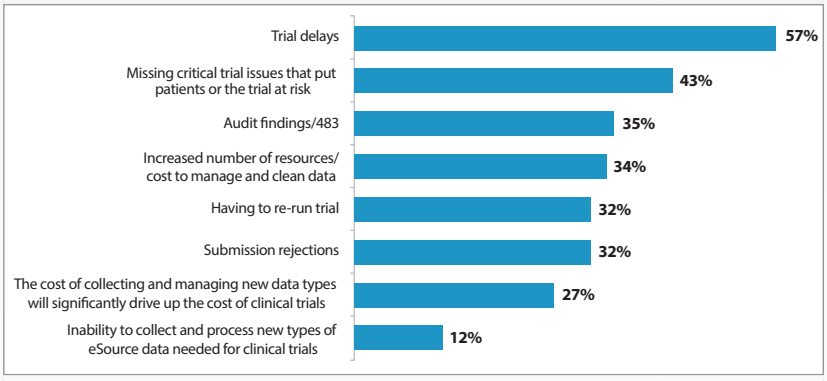
Not surprisingly, over three-fourths of respondents cited inconsistent data and missing patient data as the most critical clinical data problems to catch in clinical trials.

"Clinical teams are forced to spend time cleaning data instead of analyzing it, and they can't always see the entire picture of what is available to them; this delays the ability to make critical decisions about the trial and holds up regulatory submission," said Steve Rosenberg, general manager, Oracle Health Sciences. "Clinical researchers shouldn't have to spend time and resources on fixing data issues that technology was built to handle. Technology can, and should, be used to eliminate unnecessary manual intervention and mitigate risk so we can get therapies in the hands of patients who are waiting."

The top three risks highlighted by the research include the need for additional data reconciliation; incomplete data to determine efficacy; and patient replacements.

— Wire report

Clinical Data Challenges



Source: Oracle Health Sciences

Clinical researchers identify their most pressing data-related challenges.

Live webinar:

Thursday, October 11, 2018
11am EDT

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A Pan-cancer View of Immune Cell Activity, Immune Checkpoints, and Tumor Mutational Burden

Event overview

In addition to tumor mutational burden (TMB) and intrinsic subtypes, RNA-based assays are now available for clinical trials to measure immune cell activity in the tumor microenvironment given a tumor specimen. Our laboratory results suggest measuring immune cell type activity, key variants and mutations, and TMB all have clinical relevance pan-cancer and shape outcomes. Separately, they each provide important information about the tumor and its micro-environment and can often be combined to explain much more than any single factor individually. Therefore, there are opportunities for employing additional genomic and proteomic biomarkers to predict or explain variation in outcomes when performed by qualified laboratories.

In this webcast, we will discuss how Immune landscape signatures, TMB, immune checkpoints, and tumor subtypes are all important measurements in oncology and immunotherapy clinical trials. We will also explore how therapeutic response and key clinical endpoints, such as progression-free and overall survival, are highly associated with key genomic factors such as immune activity and TMB.

Key learning objectives

- Understand different aspects of immune cell activity and their pro and anti-tumor characteristics
- Examine advantages of multi-variable analysis of survival and therapeutic response using clinical and genomic factors and how this can lead to useful biomarkers in many distinct indications
- Demonstrate the empirically measured quantitative relationships pan-cancer between key immune-related components such as cytotoxic T lymphocytes, B cells, macrophages, checkpoints, and TMB in solid tumors

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Q&A

MID-SIZED CROs CONSOLIDATE IN SPECIALIZED THERAPEUTIC AREAS

Mergers and acquisitions in the CRO space are a common trend with large enterprises. However, consolidation is now moving toward mid-sized CROs through strategic acquisitions in specific disease indications. Synteract recently merged with Cu-Tech in order to expand its global footprint in dermatology clinical trials, and develop an operational infrastructure that allows them to better handle operating big-pharma clinical trials in the dermatology indication. In this interview, Kathleen (Kit) Ashenfelter, VP of dermatology development, and Trisha Vonder Reith, executive director of marketing communications at Synteract, discuss the Cu-Tech acquisition.

Q: What prompted the acquisition of Cu-Tech by Synteract and what does this acquisition mean for biopharma companies?

Trisha Vonder Reith: Synteract recently announced the creation of therapeutic centers of development that are focused on some of the more progressive complex areas of the biopharma industry. In continuing to deliver on the strategy of developing these highly-expert therapeutic areas, we recognized our strength in dermatology and looked for a partner that had complementary collective expertise. We established a relationship with Cu-Tech as a recognized leader in dermatology; Cu-Tech's decades of experience in this area augments Synteract's considerable dermatology expertise. It's a powerful combination that makes the combined company a leader in dermatology clinical trials management.

We are very excited about what this offers to both Synteract's and Cu-Tech's combined customer base. Cu-Tech has an incredible track record of dermatological expertise and over the years has developed some incredible relationships with sites, investigators, and thought leaders in the dermatology space. Cu-Tech's team can now offer the ability to provide clinical operations, project management, and regulatory expertise as a full service with our biometrics, safety management, medical affairs, regulatory strategy, and other services. Cu-Tech has managed more than 130 dermatology studies and Synteract has managed about 120 dermatology studies.

Q: What are the leading challenges with dermatology clinical trials?

Kit Ashenfelter: Dermatology is unique from other therapeutic areas because efficacy endpoint assessments are qualitative and subjective in many cases. They are observed visually by the investigator's trained eye versus mostly quantitative results in other therapeutic indications. It becomes really important to train the dermatology investigators to make sure that they are assessing particularly the primary efficacy parameters in a consistent manner.

In several dermatological indications that require treatments with topical products, the placebo effect often narrows the efficacy range between active and placebo. Thus, it is critical to the study's endpoints that investigators' training discern differences in improvement through validated rating scales. The challenge is in ensuring that there is rater consistency across participating investigators in a study, particularly in Phase III, when the drug should be showing distinctive efficacy results in such narrow efficacy ranges.

In order to mitigate these risks at Synteract, we ensure investigators are appropriately trained, for some indications pass a test, and are within consensus with their peers on the expectation on how they are rating the disease.

Q: How are clinical trials for dermatology evolving? What are some trends in this space?

KA: A trend that we are recently observing is that more sponsors are developing interest in patient-centric assessments, such as patient-reported outcomes or questionnaires to support efficacy endpoints. This approach takes into consideration the subjects' perspectives on how they feel they are responding and their satisfaction level with the investigational product. These patient questionnaires are not usually selected to support primary endpoints, but rather to demonstrate improvement of quality of life.

Kit Ashenfelter | Trisha Vonder Reith

There are a few indications, such as pruritus (severe itching, a symptom of many conditions) when patient questionnaires are used to support primary endpoints. Many of these questionnaires used to be paper-based; however, we are seeing a lot of questionnaires moving toward electronic devices. Currently, in most dermatology indications, the investigator global assessment is still the most common method used to support primary endpoints; but, validated patient questionnaires are becoming very common.

Q: What about working with networks and organizations in this space?

KA: The dermatology therapeutic area is a very unique community. Investigators and their site personnel involved in clinical trials know and respect one another, and there is a close personal collaboration between the sites, CRO, and the study sponsors. Many of our dermatology sites tend to be freestanding private clinics and are now increasingly becoming a part of SMOs (site management organizations). We are also working with key opinion leaders who tend to be affiliated with institutional and academic settings.

It is important for us to foster a productive relationship with our sites in order to sustain performance, such as ensuring GCP compliance and producing high quality data. We believe our personal relationship with our sites is most critical to our success as a CRO managing our sponsors' trials. Through these long-term site relationships, we are developing more collaborative opportunities resulting in improving our ability to successfully enroll and complete studies within the timelines.

— Staff report

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Navigating the Complexities of Drug-Biomarker Co-Development

Barry S. Sall, Angela X. Qu, MD, PhD

Success in developing targeted medicines means companies need a companion diagnostic strategy, the expertise, and more.

PRECISION MEDICINE

Pharmaceutical companies are investing heavily in targeted medicines, and with good reason. Tightly defined patient populations, selected via biological marker (biomarker) tests performed on cells, tissues, and blood, can streamline recruitment for clinical trials and boost success rates, helping developers improve R&D efficiency. Indeed, recent data suggest clinical trials using biomarkers—including genomic biomarkers—are twice as likely to succeed as those that don't[1] and, overall, the probability of a drug making it from Phase I to market triples when biomarkers are used in development.[2]

An accelerating understanding of cancer genetics has led to treating patients based on the precise molecular signature of their tumor(s) rather than the originating organ(s), making a biomarker strategy ever more essential for successful development efforts. For example, in May 2017, the FDA, for the first time, approved a treatment based on a common biomarker rather than on the location in the body where the tumor originated (some have called it a "tissue-agnostic" cancer indication). Pembrolizumab, a PD-1 checkpoint inhibitor, was granted accelerated approval for patients whose solid tumors have microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers and who either have failed prior therapies or have no therapeutic options.

However, developing a precision medicine that relies on a companion diagnostic test (CDx)—a test based on biomarkers that prospectively predict likely responses—to stratify patients is becoming increasingly complex due to rapidly growing knowledge about tumor biology and the swift evolution of diagnostic technologies. For these reasons, to succeed in developing targeted medicines, companies need a biomarker strategy and the expertise to make smart decisions about clinical trial design, assays, technology platforms, and collaborative partners.

Drug-CDx co-development can be successful, but it's complicated

In an ideal scenario, co-development of a drug and a predictive biomarker starts early, preferably during preclinical development, and proceeds in tandem. However, the reality of co-development is often less linear. Why?

Sometimes, the need for a biomarker to stratify a sub-population of patients becomes apparent only midway through development, requiring companies to innovate on the fly. Sometimes, the biomarker development strategy relies on a research-based or laboratory-developed test (LDT) assay for initial stages of clinical research but then must transition to a commercial assay for later stages of research and commercialization. Other times, a company that used a research-based or prototype assay to generate its clinical data finds that a commercial assay has become available during development.

Regardless of whether there's been a textbook co-development process from the start, or it has followed a less direct path, the drug and the biomarker test should obtain FDA approval at the same time. That's because the agency classifies most CDxs as Class III medical devices requiring the most stringent approval route: a premarket approval application (PMA), with the assay and drug cross-labeled. Sponsors of PMAs must demonstrate the clinical utility of the PMA device and, in this case, clinical utility is linked to the performance of the drug in the patient population defined by the CDx assay.

Further complicating co-development, basic research continues to reveal the genetic complexity of oncogenesis, and new technologies, such as next generation sequencing (NGS), are changing the CDx model from testing for single-gene mutations to mass profiling of hundreds of genes and employing other techniques, such as immunoassays.

Five steps to navigate drug biomarker co-development

Companies working in this space can better manage complexity and risk if they follow five steps:

1. Begin with a biomarker strategy

Many companies recognize that they eventually will need a biomarker strategy but may put off developing one in the early stages of R&D and preclinical work. Unsure when to initiate such a strategy or what its scope should be, smaller companies with limited budgets understandably may want more proof of concept (PoC) data before investing in a long-term strategy. However, once there is preclinical data that suggest a mechanism of action (MoA), it is time to start evaluating clinical applications, including whether and how biomarkers might play a role.

The initial version of such a strategy can be brief and expand as the drug development effort progresses. In cases where a specific biomarker or CDx has not yet been identified, the initial biomarker strategy would mostly focus on assessing biomarker candidates relevant to the drug target and pathway(s), defining the scope for exploratory biomarker interrogation, and the number and type of biosamples for collection and their management.

It's critical to select the right indication and target the right patient subpopulations, especially in the crowded oncology space (the therapeutic area in which many drug-CDx combinations have been approved). The presence of a CDx or investigational assay" to select patients will also influence clinical trial design. In some cases, regulators will want to evaluate data from both biomarker-positive and biomarker-negative patients, so that negative predictive value for the test can be determined.

An in-depth analysis of the biomarker/genomic landscape – leveraging domain experts, public data and internal records – will be required to pinpoint target patient populations and to clarify:

- The genetic mutation profiles with functional impact on or associations with your drug-target activities and intended indications.
- Other drugs that have the same MoA and biomarker associated with their absorption, distribution, metabolism and excretion (ADME) profile, including their efficacy and safety.
- Whether you need additional evidence, such as an exploratory biomarker investigation. If so, how that would be done.

A sound biomarker strategy is also rooted in knowledge about the target disease condition(s): What types of samples are obtained from subjects? How many? When are they obtained? Where are they stored? Should pre-analytical processing steps (extractions) be performed prior to storage? Are the samples stable in storage or do they degrade? Are procedures in place for labeling samples and for accountability in handling them?

2. Collect and manage human biosamples properly

Competency in biosample (i.e., urine, blood, tissue, cells, DNA, RNA and protein) collection and management is required to co-develop a drug and a biomarker test. Samples collected in early trials may turn out to be critical years later.

For example, one company recently began its clinical program using a research-based biomarker test that was never intended for commercial use. While the trials were in progress, a commercial assay was developed. The company now had a mixed bag of data: early studies that used the research assay and later studies that used the commercial assay. The company had to conduct a bridging study to prove the two assays performed equivalently. To compare the two assays and bridge the data gap, the sponsor needed enough patient samples – properly stored – from both the early and late phase studies.

For many experimental cancer agents, biomarker testing may serve purposes beyond just selecting patients. For instance, biomarker evaluation could allow deeper exploration of a new MoA. To accommodate these exploratory aims, companies must collect and store the right patient samples and ensure that well-crafted consent language allows for the use of those samples to measure biomarkers such as blood-based genomic profiling.

Proper management of human samples entails, among other things:

- Obtaining informed consent from patients for current and potential (but currently unknown) future use such as genomic testing or bridging studies.
- Banking samples for future retrieval in environments that will prevent tissue degradation.
- Building the appropriate infrastructure and IT to validate a sample's chain of custody by tracking it through the complex ecosystem of laboratories, depositories and internal research and development facilities through which it will pass in its lifespan.

3. Choose the optimal assay and technology platform

The technology platforms for biomarker testing are constantly evolving, not just for CDxs but also for complementary diagnostics (tests not used for patient selection but to improve disease management, early diagnosis, risk stratification and monitoring).

Currently driving a technology transformation, NGS can deliver a report on different mutations across a series of different genes (versus a simple yes/no status for a specific mutation in a specific gene). This provides coverage and efficiency advantages, as well as lowering costs.

Other technology platforms comprise the majority of companion and complementary diagnostics that have gained FDA approval and include:

- Real-time quantitative polymerase chain reaction (qPCR)
- Proteomics (protein, peptide, immune-cytokine)
- *In situ* hybridization (FISH) tests
- Molecular pathology (IHC) – immunohistochemistry (IHC)
- Others (imaging, metabolite)

No particular assay technology is preferred by regulators; each is evaluated on a case-by-case basis.

There are several considerations in biomarker assay/technology selection depending on the intended biomarker utility (Is it used for patient selection? Is it exploratory? etc.). Among commercially available assays and technologies, companies must choose an optimal platform and approach (e.g., from single-plex to multi-plex, from single gene to whole-genome).

For example, the FoundationOne CDx (F1CDx) is an NGS-based *in vitro*

Drug-CDx Approvals

TRADE NAME (GENERIC NAME)	DRUG SPONSOR	INDICATION	COMPANION DIAGNOSTIC (CDx)	CDx DEVELOPER	CDx MOLECULAR TARGET	APPROVAL DATE
Gilotrif (afatinib) (1)	Boehringer Ingelheim International GmbH	metastatic non-small cell lung cancer (NSCLC) with non-resistant epidermal growth factor receptor (EGFR) mutations	*therascreen*® EGFR RGQ PCR Kit (1)	Qiagen N.V.	EGFR mutations L861Q, G719X and S768I	January 12, 2018
Lynparza (olaparib tablets) (2)	AstraZeneca Pharmaceuticals LP	deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer	BRACAnalysis CDx® test (2)	Myriad Genetic Laboratories Inc.	BReast CAncer susceptibility gene (BRAC)	January 12, 2018
Tasigna (nilotinib) (3)	Novartis Pharmaceuticals Corporation	addition of treatment-free remission data to label for Philadelphia chromosome-positive chronic myeloid leukemia (CML)	MolecularMD MRDxTM BCR-ABL test (3)	Molecular MD	breakpoint cluster region–Abelson (BCR-ABL1) mRNA transcript levels	December 22, 2017
Ogivri (trastuzumab-dkst) (4)	Mylan N.V. and Biocon Ltd.	breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) with overexpression of HER2 gene	FDA-approved tests for HER2 protein overexpression and HER2 gene amplification	*(various)*	*(various)*	December 1, 2017
Idhifa (enasidenib)	Celgene Corporation	relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation	RealTime IDH2 Assay	Abbott Laboratories	isocitrate dehydrogenase-2 (IDH2)	August 1, 2017
Rydapt (midostaurin)	Novartis Pharmaceuticals Corporation	newly diagnosed AML with an FLT3 mutation	LeukoStrat CDx FLT3 Mutation Assay	Invivoscribe Technologies Inc.	fms-like tyrosine kinase 3 (FLT3)	April 28, 2017

(1) Supplemental application for a new indication on the label. (2) Granted regular approval from original accelerated approval.
(3) Label update. (4) Biosimilar of Herceptin

Source: Sall

Figure 1. Recent FDA approvals of drugs with a companion diagnostic.

diagnostic (IVD) device approved in late 2017 for detection of substitutions, insertion, and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures, including microsatellite instability (MSI) and tumor mutational burden (TMB). It is currently on the label of 17 different targeted medicines to treat five types of cancer. (The F1CDx assay is a single-site assay performed at Foundation Medicine, Inc.).

4. Find the right partner(s)

Selecting an assay development partner is the next critical decision. A good partner should have the technical capability to develop a robust and cost-effective assay in a timely manner. It needs internal systems compliant with the U.S.'s Quality System Regulation (QSR), the European Union's IVD Regulation and any other jurisdictional regulations.

The partner also should possess an assay platform consistent with the needs of the drug developer and its commercial stage customers. For example, if it is anticipated that laboratories will need to evaluate large numbers of patient samples per day, the assay platform should be compatible with high throughput. The size and geographic distribution of the partner's installed base of instrumentation should also be considered during the selection process. Generally, manual and semi-automated assays can be developed more quickly and less expensively than assays that utilize high throughput instrumentation.

Sometimes, companies discover they need a biomarker – and an IVD development partner – relatively late in the development process. In such cases, one option is to leverage an existing relationship with a contract research organization (CRO), having it serve as the point of contact to manage complex CDx partner development issues.

For example, a company scouring its unexpectedly weak Phase I and II efficacy data began to see strong signals of activity when it segmented the patient population according to a biomarker. The presence of this biomarker could clearly identify the patients most likely to respond to the drug. Already in Phase II development, the medium-sized company, not equipped to develop its own IVD, faced a host of pressing questions including how to incorporate the biomarker/CDx test into the existing development plan, would the validated assay be available, and how to find a qualified partner for developing the IVD.

In the U.S., a commercial CDx assay must be developed in accordance with the Design Control provisions (21CFR 820.30) of the QSR. The new EU IVD Regulation will require compliance with the ISO 13485 Quality System standard and other requirements. Compliance with these regulations requires multiple standard operating procedures (SOPs) and considerable documentation once the assay development process is underway. This is one reason that drug developers rarely develop CDx assays internally, usually engaging diagnostic development partners that already have systems and staff in place to generate the necessary documentation.

Companies must determine whether there is a commercially available assay that can be used. If not, can they find an assay not yet commercially available but already in development? (Caveat: It is often difficult for outsiders to find out if an investigational assay exists because assay developers generally do not discuss them publicly.) In either case, a company will need to work out an arrangement with a manufacturer if it is going to use it to select patients for clinical trials. If an assay is already approved for the relevant analyte – for another drug or for another disease – an investigational device exemption (IDE) may still be necessary if assay data will be used to select subjects for treatment with the investigational drug.

5. Validate biomarkers and regulatory options

Once there is enough data to analyze, computational and other analytical techniques can be used to identify informative biomarkers. Biomarker candidates must be interrogated rigorously to inform CDx development.

If there is no existing assay that measures the relevant biomarker (that is, you are developing a novel drug with a novel MOA that will require a novel diagnostic test), there are many regulatory considerations. A novel CDx faces the same regulatory hurdles as any diagnostic tool: you will have to demonstrate that it performs properly in terms of specificity, accuracy, precision (with reproducibility and repeatability), and clinical utility.

In an attempt to streamline the CDx process, the FDA recently released two guidances with recommendations for designing, developing and validating genetic and genomic-based tests, including IVDs, NGS technology, and other precision medicine devices.

The April 2018 draft guidance, Investigational *In Vitro* Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry, provides what could be a simpler path for companies to evaluate their assay risk status (that is, is an IDE needed?). Assays can now be considered during the investigational new drug (IND) application review, rather than in a pre-submission meeting with the Center for Devices and Radiological Health (CDRH). This could potentially reduce the time needed to prepare for and engage in an extra meeting, but still requires that a comprehensive data package be included in the IND filing.

In the U.S., a detailed analysis of the regulatory process and commercial landscape associated with any one CDx may suggest that the LDT route may be more appropriate, at least for early commercialization. Currently, LDTs do not require FDA approval and an LDT assay can utilize any assay technology (including when there are multiple biomarkers that need to be tested and validated at the protein/cytokine level).

The advantage of an laboratory development test (LDT) is that it can be made available quickly, without the need for FDA approval. The disadvantages include: 1) In order to be considered an LDT, the assay must be developed, validated and performed in the same CLIA high-complexity certified clinical laboratory; it cannot be performed in multiple laboratories; 2) The enforcement discretion that FDA is currently exercising with respect to LDTs could end with an administrative policy change; and 3) Reimbursement for LDT assays may be more difficult to obtain than for PMA-approved assays.

Even when there are commercial assays available (such as the PMA-approved PD-L1 assays) in some limited cases, it may be possible for FDA to review a CDx assay via the de novo classification process.

Even if a relevant CDx already is approved (with a different drug), before a company can cross label their new drug and the existing CDx assay, a new PMA that mentions the name of the drug in the assay labeling must be submitted and approved by FDA.

Risks and opportunities abound in a fast-changing environment

Biomarkers not only help identify patients who will receive meaningful benefits from a drug, they also identify those who won't, reducing the risks unnecessary treatments pose to patients and the costs ineffective ones impose on payers.

Because of their obvious efficiencies and superior efficacy, the biopharmaceutical industry will continue to focus on targeted medicines in cancer and other therapeutic areas. As a result, competing successfully in this space will require developers to perform at the highest levels of strategic, operational, and technological excellence.

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References

1. Wong, C., Siah, K. and Lo, A. (2018). Estimation of clinical trial success rates and related parameters. Biostatistics. [online] Available at: https://academic.oup.com/biostatistics/advance-article/doi/10.1093/biostatistics/kxx069/4817524 [Accessed 10 Apr. 2018].

2. Thomas, D. W., Burns, J., Audette, J., Carrol, A., Dow-Hygelund, C., & Hay, M. (2016). Clinical development success rates 2006-2015. San Diego: Biomedtracker/Washington, DC: BIO/Bend: Amplion.

New ICH Guidelines Address Industry Inefficiency

Crissy MacDonald, PhD

A review of new updates to ICH E6 (R2), the resulting challenges, and recommendations for compliance that organizations can implement.

RISK-BASED MONITORING

Although the pharmaceutical industry has always incorporated risk-based processes, the ICH E6 (R2) addendum now mandates that clinical trial operations also include risk-based approaches. Based on the latest research, and The Avoca Group's experience helping companies implement remediations, a fundamental shift in mindset is necessary in order for the industry to properly address the required changes. This article is a review of the key changes in ICH E6 (R2), discussion of the challenges organizations are facing, and presentation of actionable recommendations for organizations to implement now.

Key changes to ICH E6 (R2)

With the evolution of clinical trials and the supporting technology and processes, there are new opportunities to increase efficiency and focus on relevant activities. Recognizing the importance of this, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) released a revision to its guidelines to: "encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results."

In addition, to support innovative processes, the standards for essential documents have been updated to include process and procedural documentation outside the standard definition of required documents.

Risk-based strategies

The strong risk-based component to the new regulations recommends oversight commensurate with the important risks. It is almost impossible to monitor the nearly one million data points collected in an average Phase III trial. Therefore, identifying the important data points—for subject safety and reliability of the results—can help prioritize the data monitoring strategy.

To have successful risk-based strategies, the organization must also have an appropriate quality management system (QMS). This system should be responsive to the trial needs, include documentation of the rationale for the chosen strategy, and have clearly defined roles and responsibilities.

Risk planning

With the updated regulations, the sponsor and investigator(s) retain accountability for trial quality, necessitating effective oversight and a good understanding of risk management. All parties participating in the operation of the clinical program must agree and understand the expectations for each role—clear documentation of this is required.

When outsourcing study management, the sponsor organization must maintain a key role in pre-study risk planning. Although the CRO can be responsible for risk planning, the CRO needs to obtain agreement from the sponsor on the critical factors for quality, defined thresholds, and mitigation plans.

Quality management

Section 5.0 in ICH E6 (R2) outlines the quality management recommendations, focusing on subject protection and the reliability of the trial results. Information essential to decision-making should be collected.

Quality by design (QbD) practices minimize risk through proactive planning—using current knowledge as well as historical data about the organization and inves-

tigational product. The planning process should identify which risk signals can be detected early and outline the associated mitigations (including an investigation of the root cause). Then, findings from any corrective actions, preventative actions, and mitigation should be built into the process. Finally, the outcomes of this initial planning phase can be used to make quality-focused decisions.

Electronic systems

To ensure quality data, validation and quality control are required using qualified users and SOPs that cover system setup, installation, and use.

Any electronic data handling and/or remote electronic data systems must be validated, meaning the system conforms to the established requirements for completeness, accuracy, reliability, and consistent intended performance. Sponsors must determine and document that specific requirements of the computer system can be consistently fulfilled from design until system decommissioning/transition to a new system.

The validation approach should be based on a risk assessment that considers the intended use and the potential to affect the protection of subjects and reliability of trial results.

RISK ASSESSMENTS DRIVE THE VALIDATION APPROACH

A computer database that provides lab results to the medical monitor for analysis may need to be validated with more scrutiny than a database that contains the contact information of all investigators.

Serious breaches

Regulatory authorities want to know when something has gone wrong, and it is best to be up front when non-compliance is detected. Therefore, make sure to inform regulators when non-compliance is a serious breach of protocol or good clinical practice (GCP) guidelines.

Essential records

According to the updated guidance, "Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements."

Therefore, it is important to document what you're doing and how you perform your risk management processes, including the following components: monitoring plan, integrated quality management plan, quality management plan, and the outcome of and actions taken because of centralized/statistical monitoring.

All procedures and processes within clinical trial execution should be documented in the trial master file (TMF) and undergo periodic review. ALCOA-C (Attributable, Legible, Contemporaneous, Original, Accurate, Complete) provides some crucial concepts regarding source documentation and helps ensure confidentiality, credibility, accuracy, and validation.

Key challenges with implementing ICH E6 (R2)

ICH E6 was updated because of the increased use of technology in clinical trials, making real-time feedback of processes and data reviews more feasible. Regulators now require the use of safe technologies to more efficiently and effectively design and conduct the clinical trial. However, implementing these new requirements can seem daunting—the use of more proactive approaches represents a shift from typical industry operation.

ICH E6 was updated because of the increased use of technology in clinical trials, making real-time feedback of processes and data reviews more feasible.

Based on a survey The Avoca Group conducted with 80 respondents from the attendees of ExL's 7th Clinical Quality Oversight Forum in 2017, the reported challenges with moving toward ICH E6 (R2) fit into three buckets: change management, oversight, and data-driven decisions.

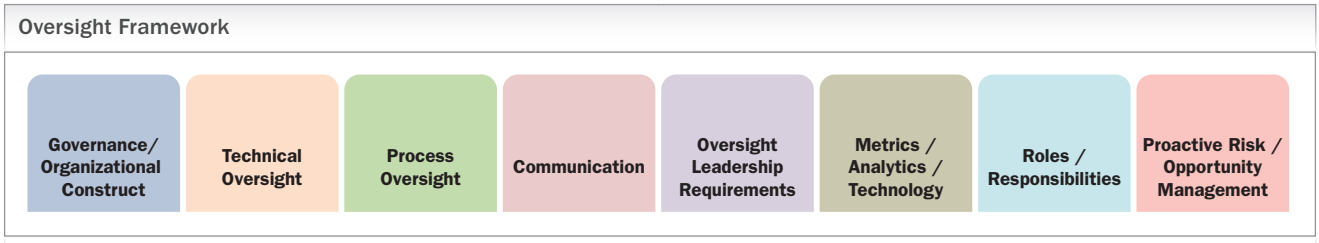
Change management

Organizational change management is one of the primary challenges with the new regulations. Organizations are a complex mix of processes, people, and management. Operational staff often recognize the impact of quality on the day-to-day level, while top-level executives often view the big picture, making it difficult to get leadership buy-in. A one million-dollar question in the industry remains: the comparison of the cost of proactive risk mitigation vs. the cost if the risk actually becomes an issue—this ultimately affects the bottom line.

Quality ownership is also changing; ICH E6 (R2) mandates that everyone is part of the quality process and process improvements throughout the entire clinical trial. Therefore, quality is no longer just the quality assurance (QA) team's concern. Although changes to internal processes are required for compliance, the resourcing required to update these processes often competes with current priorities and daily tasks.

Through my interactions with companies, I've found that employees "not knowing" if the company is currently ICH E6 (R2) compliant represents a lack of understanding throughout the entire organization of its importance, its meaning, and the difference from current operations. We need to start recognizing that this isn't just about quality—it is about creating more efficient, risk-based clinical trials that ultimately have a much better outcome for the patients participating in the studies.

To address these challenges, some companies have found that getting leadership buy-in and determining who "owns" quality make all the difference. However, quality is not a siloed function, and the entire team is required for successful changes. It's time to shift the idea of quality as a burden (a continual request for funding in fear



Source: MacDonald

Figure 1. Eight quality oversight components defined by the Avoca Quality Consortium.

of compliance and inspection findings) to one of opportunity. For example, think about if you moved away from 100% source data verification (SDV) toward a risk-based approach focusing on the data points with the greatest impact on key study endpoints. You've freed up resources—where else could those be used? Where else could efficiencies be gained?

Other companies have found it useful to view change management as a journey, with corresponding process maps. These maps are function-specific (e.g., technology, clinical operations) and can be used to visualize when you've reached the end of the journey. Building a brand around the initiative builds enthusiasm for the task, while commitment from leadership helps reach across the organization and keep the momentum going. Then, provide rewards for proactive, solution-finding activities. Empower ownership of the initiatives within each function.

Because reaching the right level of oversight can be challenging, risk reviews can help to achieve the optimal balance.

Oversight

Effective oversight helps ensure alignment of sponsor and provider processes for clinical trial execution (which is often lacking) as well as cross-functional alignment on their quality-related priorities.

The level of oversight needs to be appropriate. With very high-level oversight, you jeopardize missing the risk indicators for patient safety, regulatory findings, and the organization's reputation. Micromanaging sacrifices the intended efficiency gains from outsourcing.

Sponsors need to ensure that key activities are being performed by adequately trained resources—within both the sponsor organization and external providers. Therefore, training is critical and ongoing. It is imperative to provide training on the SOPs to all members within the partnership to make sure everyone is on the same page. In addition, staff who are overseeing the provider should be trained in their oversight expectations, including when to escalate issues.

Having the right people performing the right tasks at the right time can help minimize duplication of effort, avoid micromanagement, ensure accountability, and enhance the successful delivery of the outsourced project. To ensure efficient task execution and effective oversight, the roles and responsibilities within the organization and between the sponsor and partners need to be clearly articulated. Proactively define the roles and responsibilities before the project work begins and then refine and enhance periodically to reflect newly recognized risks or issues.

Through proper planning, the processes that will be followed by the sponsor and provider will align to the clinical trial's SOP. Document a formal agreement, through a quality agreement or joint quality management plan, to ensure a clear understanding. Store this agreement in the trial's TMF. Revisit the document frequently throughout the trial to update, refine, and modify as necessary—making sure to document these subsequent reviews.

Oversight tools have been developed by several organizations, including the Avoca Quality Consortium (AQC). The AQC, through its 90-plus member organizations (sponsors, CROs, and providers), created a framework of eight swim lanes of quality oversight components (see Figure 1). Within each of these swim lanes are industry standards, documents, and templates that help organizations determine the right level of oversight and if their oversight is meeting the intended outcomes.

The supporting documents within each of these components are scalable to each study. Because reaching the right level of oversight can be challenging, risk reviews can help to achieve the optimal balance.

Before the study starts, identify the quality metrics that are necessary to track the key risks and issues as well as the corresponding metric taxonomy. Rather than just having a collection of metrics, you can identify the corresponding thresholds that indicate some action should occur or a risk is near realization. Effectively, these metrics are warning signs and a way of proactively mitigating the risk. One key to a successful partnership is making sure that those with shared learnings, both internal and external to the program, are preventing recurring or preventable errors.

Data-driven decisions

Knowledge of the data required to make decisions about patient safety and trial efficacy is paramount to efficiently using the vast amounts of data collected. Early in the process, identify and document the quality metrics, and more specifically, quality tolerance limits (QTLs) that need to be accessed and integrated as well as the corresponding action that must be performed.

Quality Tolerance Limits (QTLs)

WHAT:	WHEN:	HOW:
A QTL is a level, point, or value associated with a parameter that, when a deviation is detected, should trigger an evaluation to determine if there is a possible systemic issue. • **It is a trial-level parameter, not a patient-level parameter. Examples include inclusion/exclusion protocol violations, incomplete/missing endpoint data, and AEs/SAEs of special interest.** • **QTL parameters are absolutely critical to basic trial integrity, patient safety, and the primary endpoint. In contrast, a key risk indicator is something that is nice to know: e.g., the recruitment rate is important to understand if your study is on track, but regulators will not be concerned if your recruitment rate is slower than you want it to be.** • **The number of QTLs for a clinical trial should be limited (3-5).**	**QTLs need to be defined at the planning level of the trial in coordination with risk assessment activities.[1] The plan should also include strategies for monitoring these parameters, determining the root cause, and addressing any deviations.**	**It is important to define the expectations and variability that are inherent in executing the clinical trial to accurately define the limit that might indicate systemic problems. Therefore, QTLs should be based on:[1]** • **Medical and statistical expert knowledge of similar trials** • **Historical data from similar trials** • **Statistical methods and modeling** • **The known or anticipated risks of the agent under study, based on the mechanism of action or other parameters**

Source: MacDonald

Table 1. Identifying quality tolerance limits to make data-driven decisions.

TransCelerate has excellent resources[1] to better understand QTLs—developed as part of its risk-based monitoring initiative. Briefly, the goal of a QTL is to detect systemic risks—those that will affect the study and make it very hard to draw the right conclusions from your results.

In the initial stages of implementation, there will likely be limited availability of historical data of the systemic or random nature of observed issues. In these cases, the use of published data to define QTLs is encouraged. For new indications or compound classes, extrapolation of experiences from similar indications or trials may be appropriate. Similarly, while updating QTLs is not ideal and the number of updates to QTLs is expected to decrease to zero as experience with QTLs grows, it is understood that modifications may be required during the clinical trial. This is acceptable as long as sufficient rationale and documentation are provided in both trial documentation and the clinical study report (CSR) to justify the changes in the QTL. Also, regulators want to know that you have a documented action and will conduct root-cause analysis if something does happen.

Then, ensure that you have the right technology tools available to evaluate the risk; the definition of "right" in this context means having real-time access to data and analyses, while matching the economy and efficiency to the scale of the organization and studies. Real-time decisions rely on the ability to deliver data from multiple systems in a format that's comprehensible to humans, ideally in easy-to-use dashboards (see Figure 2).

For all three of these areas, the key message is one of continuous improvement and avoiding repeated issues. Perfection is not expected from the start; instead, by continuously improving practices and procedures and documenting any changes throughout the trial duration, it will be easier to comply with ICH E6 (R2).

Technology Tools to Evaluate Risk

Source: MacDonald

Figure 2. Data from multiple sources must be integrated to drive informed decisions.

Actionable recommendations for moving forward

A question I am frequently asked is, "How do I get my organization to move forward with implementation?"

My response: Start at the top, by obtaining commitment from the senior management team. The goal is to build an organization committed to quality, not just within the QA group. Instead of commending the project manager who stays late fighting fires, commend the project manager who escalated the risk that was about to become an issue. Then, you change the message regarding the future state of the organization.

Start the risk assessment at the protocol development stage and assess the risk from the patient's perspective as you walk through

the trial. The Medicines and Healthcare products Regulatory Agency (MHRA) nine-question framework is really useful for this purpose. If your quality resources are limited, start by reviewing the current SOPs and identify where there are clear gaps from the new requirements. This can be performed internally or outsourced to a consulting group. Then, prioritize the gaps in order of importance based on the risks you are most concerned with mitigating. Once you are sure your SOPs are compliant, work on developing a right-sized holistic QMS for your organization. Electronic systems are not an absolute requirement, but ICH E6 (R2) does assume that companies can perform "real-time" assessments of risk-based on rapidly available data, metrics, and information.

See the data. We often focus on the next milestone (e.g., first patient in, all sites activated, database locked, inspection preparation), and we forget to pay attention to the indicators that might show when a problem is coming. Only collect the metrics that are actionable—move beyond the data specific to recruitment and data cleaning status to the data that are timeline-provoking. Finally, learn to implement your pre-determined action plans when the data starts to stray from the norm.

There are also tools available to help take a systematic approach to complying with ICH E6 (R2). At Avoca, we mapped tools developed in collaboration with the AQC to the 12 steps outlined in the ICH E6 (R2). These tools reduce the amount of resources needed to develop, execute, and document your QMS.

Summary

Quality remains a crucial component of clinical trials—to ensure patient safety and data integrity. Guidelines such as ICH E6 (R2) are helping to formalize and standardize quality components, while at the same time recognizing that adaptation to new knowledge is a key consideration. To get started, take a close look at your organization's quality culture, start with your existing processes, and determine the scale of a QMS that will enable real-time monitoring and analysis but that is also suitable and manageable for your organization.

Crissy MacDonald, *PhD, is Executive Director, Client Delivery, The Avoca Group*

Reference

1. TransCelerate Biopharma, Inc. Risk-based quality management: quality tolerance limits and risk reporting. 2017.

A United Front for Better Pediatric Clinical Trials

David Bowser, Martin A. Graham, PhD

Forming strategic alliances and collaborating to optimize study design can significantly improve pediatric drug development.

Great opportunity exists for the research community to rally around the industry's most precious patient population: children. The good news is that pediatric drug development is ripe for advancement.

In recent years, medical professionals have witnessed a significant change in the philosophical dynamics surrounding pediatric clinical trials. Instead of protecting children "from" research, industry efforts are now concentrated on protecting them "through" research. This shift has manifested itself in such U.S. legislation as the Pediatric Research Equity Act (PREA), which requires companies to assess the safety and effectiveness of new drugs/biologics in pediatric patients, and the Paediatric Regulation established by the European Union in 2007.

> To improve the pace of development for this important market segment, stakeholders must work collaboratively to optimize study design for dual adult/pediatric populations.

These drivers could open the door to new therapies that vastly improve long-term population health and quality of life. Yet, pediatric drug formulation, trial design, and dosage selection are characteristically complex, and many contract research organizations (CROs) lack specific expertise in designing clinical trials to serve younger populations.

To improve the pace of development for this important market segment, stakeholders must work collaboratively to optimize study design for dual adult/pediatric populations, as well as promote patient enrollment plans that make the best use of limited resources. Forward momentum will rely heavily on strategic alliances that bring together the high-level expertise needed to address efficient clinical trial design, regulatory compliance, and protections for younger patients.

Understanding the nuances of pediatric drug development

Supply and demand are sizeable issues for pediatric clinical trials. Many children's illnesses fall within the orphan disease category, impacting a small percentage of the population, often across a large geographic footprint. This characteristic alone illustrates the need for a broader patient recruitment reach within pediatric clinical trials.

CROs engaged in these studies often compete for the same patients, which is one reason why the FDA recently released new guidance to encourage greater collaboration that supports evaluation of multiple products in a single trial. While this move is a promising development, the current dynamic still poses significant challenges for many studies requiring a pool of young patients.

For example, studies that recruit from large geographic areas usually involve oversight from multiple regulators such as FDA and the European Medicines Agency (EMA). As such, CROs must ensure clinical trial design addresses the requirements of all governing bodies—a challenging proposition since pediatric requirements are continuously evolving and typically are not harmonized across borders. Often, trial design must

follow the most stringent rules regardless of location to support clinical efficacy as well as standardized, operational efficiencies within a single plan.

> Every trial is unique, which means trial partnerships cannot take a one-size-fits-all approach to collaboration.

Satisfying the need for operational consistency, quality, and data integrity throughout the clinical development process requires integrated, specialized global pediatric drug development resources able to leverage cutting-edge pediatric trial techniques—such as computer-based modeling and simulation—and optimal global clinical trials infrastructures. These nuances, coupled with the need for extra flexibility and safeguards for younger patients, often equate to greater risk in terms of cost and successful trial outcomes. For instance, 42% of recently completed pediatric trials failed to attain product labeling for use in children due to failure to establish safety or efficacy.

Fortunately, there is a better way.

Building a better pediatric clinical trial

The good news is that strategic industry alliances can reduce risk and improve the outlook for pediatric drug development. CROs that specialize in pediatric trials are partnering with global CROs that bring together the right combination of therapeutic expertise, trial design knowledge, and geographic reach to ensure efficient, effective operations across multi-population, multi-center, multi-national studies.

Every trial is unique, which means trial partnerships cannot take a one-size-fits-all approach to collaboration. However, such alliances can achieve success by creating cross-functional teams consisting of scientific, operational, and technical resources within both organizations, depending on the specific needs of the sponsor. A project manager from a global CRO, for example, might lead a blended team of pediatric pharmacokinetic/pharmacodynamic (PK/PD) and regulatory experts, with support from the global CRO's trial monitoring and data management experts.

Collaborative efforts like these are exploring effective ways of minimizing the number of children needed for participation as well as their exposure to study elements such as medications and tests. A combination of advanced pharmacometric modeling and clinical trial simulation technologies—such as PK/PD modeling, physiologically-based PK (PBPK) modeling, and population PK analysis, for example—can help facilitate efficient pediatric trial design and minimize patient numbers and invasive procedures.

Often, economies of scale also can be achieved by drawing on the groundwork laid by late-state adult trials. The key is using the combined resources of global and pediatric CROs to get in front of adult trials to ensure considerations for pediatric research—including identifying data and formulation needs—are built into the initial design. A CRO specializing in pediatric clinical trials can bring pediatric formulation and juvenile toxicology expertise to the table, while a global CRO can incorporate its more extensive trial design knowledge.

Clinical trial design that considers both adult and pediatric populations produces numerous wins for sponsors. When adult clinical trials draw from their own data sets to support pediatric studies, the opportunities for reducing patient exposure, maximizing safety, and improving operational efficiencies increase exponentially. In addition, trial sponsors can leverage the benefits of incentive programs currently offered by the FDA and EMA. Organizations that are willing to embark on a pediatric clinical trial earn eligibility for a six-month exclusivity extension for both the adult and pediatric version of a product—a significant bottom-line consideration for certain products.

The industry is making notable strides to overcome barriers to, and speed the pace of, pediatric drug development. While the commercial opportunity is certainly improving, the reality is that the stakes are high in terms of medical need across all therapeutic areas. Children represent the industry's most vulnerable and treasured patient population, so the value of greater collaboration and cooperation among stakeholders speaks for itself.

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How to Avoid Common Pitfalls of Market Landscaping

Comprehensive market landscaping is crucial in the effort to de-risk the expensive, long-term strategic bet on a disease area.

An Nguyen
Head of Strategy, H1

Developing a new drug is a time-consuming and expensive proposition: on average, it takes $2.5 billion and 10-plus years, according to the Tufts Center for the Study of Drug Development. With costs and stakes that high, biopharmaceutical companies simply cannot have too much information about the market they are planning on investing in.

Market landscaping: Know the market well

Market landscaping is extensive, objective research that explores the target market. Regardless of the industry, market landscaping generates information about market size, market share, trends and dynamics, the competitive environment, risk factors, and barriers to entry.

Market landscaping in the pharmaceutical industry goes deeper to include detailed scientific and clinical knowledge about the therapeutic area unmet patient needs and perceptions, the cause of disease and its impact on the patient's physiology, prescribing data, current treatment regimens and how they fall short, approaches competitors are using, as well as data from ongoing clinical trials. In short, any and all information that will help draw a detailed picture of what drives the market for a specific therapy and what roadblocks could make entering that market a losing proposition.

Market landscaping pitfalls to avoid

Comprehensive market landscaping includes disparate data sets from primary and secondary sources and is a time-consuming process that requires domain expertise and commitment. Common pitfalls of do-it-yourself (DIY) market landscaping are:

- Missing relevant clinical data by only including U.S.-based clinical trials. ClinicalTrials.gov is a terrific resource that covers all 50 states as well as trials abroad, but double-checking using the WHO International Clinical Trials Registry Platform can fill in the gaps.
- Missing companies in stealth mode. These organizations are flying under the radar and, therefore, information will be hard to find. However, even these companies leave digital breadcrumbs in the form of review articles, news releases, patent applications, and even on their social media feeds.
- Ignoring the failures. You can learn a lot from trials gone awry: was it toxicity that killed the compound, patient recruitment or compliance, side effects, funding issues? Knowing what did not work helps you avoid making the same mistake.
- Ignoring history. The latest protocol and paper are certainly the most relevant, but there are important lessons to be learned from changes a sponsor made to enrollment sites, patient stratification, outcome measures, etc. that can provide valuable insight for your market assessment.
- Making your market landscaping a snapshot rather than a living, changing document. New information is released every day, new trials are registered and revised daily, making market landscaping an ongoing project.

Market landscaping resources

If you do your own market landscaping rather than hire a professional firm, here are some helpful resources and suggestions:

- Identify existing products and companies: AdisInsight, ClinicalTrials.gov, WHO International Trial Search Portal, DrugBank, LinkedIn.
- Collect product and company updates: news releases (Google News, PR Newswire); conference abstracts, Google Scholar, industry conference websites; investor presentations (SEC filings, company websites, conference presentations.)
- Dig into the science behind the products with clinical trial design, e.g., clinical trials registry, published protocols in conference abstracts and journals.
- Stay on top of the landscape with Google alerts, RSS feed for Clinical Trials, and calendar reminders for the next expected readouts.

Comprehensive market landscaping is a crucial component in the effort to de-risk the expensive, long-term strategic bet on a disease area. It takes analytical rigor, an ability to connect disparate facts, and a creative mind to connect objective facts, data, and information with intangibles like emotional factors that influence patients in their decision-making. The rich trove of information created in market landscaping will help a pharmaceutical company draw an accurate picture of their target market and identify key opportunities.