

# APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT



## RISK MANAGEMENT

A ROADMAP FOR  
RBM AND RBQM  
IMPLEMENTATION

## R&D OPTIMIZATION

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# For AD, Non-Pharma Efforts Becoming More Critical



**LISA HENDERSON**  
Editor-in-Chief

The Phase III failure and discontinuance of Biogen's aducanumab for Alzheimer's disease sealed the fate for drug development concerning the amyloid "plaque" build-up theory around the condition's cause. As Dr. RJ Tesi explained in this article, <http://bit.ly/2LgaHze>, amyloid "went from being a biomarker of the disease to the cause of the disease"—even when data to prove this was lacking. Tesi and others believe it's time to rethink what actually is Alzheimer's disease.

Theories abound. Alzheimer's as an immunologic disease caused by neuroinflammation; Alzheimer's caused by infection, metabolic disorder, or environmental toxins—all with the underlying connection of aging. Alzheimer's also might not be one disease, and like cancer, would need combination drugs to effectively treat it. Factor in, again, the lack of biomarker or effective diagnosis—for example, vascular dementia and Lewy body dementia exhibit as Alzheimer's in patients—as well as the crisis of clinical trial enrollment, and the research paradigm looks grim.

Last fall, I spoke with George P. Sillup, PhD, associate professor, pharmaceutical and healthcare marketing at Saint Joseph's University, about non-pharmaceutical interventions in Alzheimer's. According to Sillup, there are 1.3 million nursing home residents, and up to half have some kind of cognitive impairment. While one might assume that it would be easier to conduct a clinical study or enroll through or in a nursing home, that is not the case. Sillup says there is a hesitancy among the facilities,

which have clients that don't get regular family visits or have relegated their powers of attorney. Also, according to Cherian Verghese, MD, a neurologist and medical director and principal investigator of Keystone Clinical Studies, clinical trial enrollment is difficult because of a lack of awareness, as well as the separation between healthcare and clinical trials, which does not foster collaboration of care.

For those that work for or with nursing care facilities, the lack of pharmaceutical interventions for Alzheimer's means a greater reliance on non-traditional medicines, or physical and mental exercise. Soffy Vilson, chief nursing officer for Parker Life, an aging services organization, says they work to stimulate the elders' brains and engage with them often. "We pride ourselves on taking the time with their home visit. We ask how did they live? How are things arranged in their house? Where are their pictures? How is the bed positioned? And we try to replicate that in their new environment." Vilson believes the increased attention on exercise, diet, and environment provides a necessary holistic approach to care.

Susan Cade and Tatyana Shargorodsky, founders of Senior & Chair Ballet, are firm believers that movement and exercise is key to longevity and happiness for all elderly people, not just those with Alzheimer's. But for those that need memory care, Cade and Shargorodsky have witnessed first-hand the changes those individuals experience listening to music, moving their hands, or singing. "Often, they are isolated, or they are experiencing agitation or fear or anxiety because of their condition," says Cade. "But during these sessions, their body language changes. They are distracted from their pain or isolation."

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IMAGE SOURCE/GETTY IMAGES; KIPARGETER/SHUTTERSTOCK.COM

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## WASHINGTON REPORT

### MORE EFFICIENT, INFORMATIVE CLINICAL TRIALS IS THE GOAL OF FDA LEADERS

In his two years as FDA commissioner, Scott Gottlieb promoted policies and programs to streamline clinical research to facilitate the development of new medical products at reduced costs. Gottlieb repeated this theme in his farewell talk to agency staffers on April 4, where he included on his list of accomplishments that FDA took “new steps to modernize the development process for novel medical technologies” such as gene therapies, targeted drugs, and regenerative medicine.

At the same time, Richard Pazdur, director of FDA’s Oncology Center of Excellence (OCE), urged developers of cutting-edge cancer therapies to collaborate more in developing biomarkers and establishing platform trials to gain efficiencies in testing cancer treatments. With a limited number of patients suitable and willing to enter clinical trials to test new PD-1 and PD-L1 inhibitors, Pazdur advised companies to work together more to avoid waste in developing remedies that are very similar to one another. Too often sponsors conduct multiple Phase III trials using similar agents and a common comparator, Pazdur complained at the recent annual meeting of the American Association for Cancer Research (AACR).

Because inefficient testing can lead to very costly therapies, Pazdur further encouraged researchers in China and other regions to seek U.S. approval of their similar therapies to inject competition into the U.S. oncology market. Pazdur suggested that FDA could approve a foreign drug based on clinical data from China that meets quality standards, and that a streamlined development strategy may

be supported by earlier FDA experience in reviewing and approving related applications.

#### Next stage: Knowledge management

Support from FDA leaders for adoption and confirmation of biomarkers and surrogate endpoints echo long-time admonitions from Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), who regularly urges research sponsors to adopt more streamlined research practices. Moving forward, a new “knowledge management” approach to new drug testing and regulation promises further gains in streamlining drug development. Under this CDER initiative, sponsors will submit applications that present data in a structured format so that the information on a new therapy can be transmitted to teams of agency experts for timely and efficient assessment.

The aim, explained Woodcock at the April Biostatistics, Industry & Regulator Forum sponsored by the Drug Information Association (DIA) and FDA, is to shift sponsors away from long, narrative documents filed in PDF format that are repetitive and often bury the important issues. Instead, CDER assessment teams composed of medical reviewers, pharmacologists, statisticians, pharmacists, and other specialists will examine data to answer specific questions relevant to the product under review.

Woodcock is finalizing this new assessment process to handle a surge in submissions arising from important advances in biopharmaceutical science, as well as the digital revolution that has expanded exponentially the data and information supporting biomedical research. Our understanding of clinical pharmacology, and the vast amount of data from gene sequencing, she commented,

along with greater scrutiny of the value of new medical products, require “a new approach” in providing an assessment—not a review—of new drug applications (NDAs) and biologics license applications (BLAs).

To be able to assess efficiently a rising number of applications for increasingly complex therapies, review teams will identify key issues during the investigational new drug (IND) stage to be able to focus on those items in the application more efficiently and with appropriate expertise. The resulting assessment document will present a benefit/risk evaluation, the drug development program, key issues, and recommendations. Ideally, CDER teams will finish this initial assessment midway through the review period to leave ample time for FDA and the sponsor to discuss post-market research commitments and the need for a REMS (Risk Evaluation and Mitigation Strategy) well before approval deadlines. This will lead to “high quality, more uniform work products,” Woodcock said, “with fewer surprises and last-minute changes.” And the process should be more transparent and provide advisory committees with clear issues to address.

Implementation of this new assessment process coincides with a significant reorganization of CDER’s Office of New Drugs (OND). It will expand from six to eight offices to better provide patients and researchers with identifiable experts in leading disease areas: neuroscience (including pain and addiction); inflammation/immunology (rheumatic conditions, transplant therapies); internal medicine (diabetes, hematology); oncology; human reproduction (urology, OB-GYN, pediatrics, maternal health); over-the-counter (OTC) drugs; and other treatments (ophthalmology, medical imaging, compounding).

OND also will have a centralized project management group to ensure that all divisions and teams follow consistent processes and to help external stakeholders and other FDA operations identify appropriate contacts. OND is trying out this team approach on a few applications and hopes to have it in place by the end of this year.



— Jill Wechsler

### FDA NOTES

*The FDA recently released the following industry guidance documents:*

**4/11/19:** Pharmacogenomic Data Submissions

**4/4/19:** REMS: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary

**3/25/19:** Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research

**3/22/19:** Rare Diseases: Natural History Studies for Drug Development

**3/19/19:** Pediatric HIV Infection: Drug Development for Treatment

## EU REPORT

**WEAPONIZING CANCER AS A EUROPEAN ELECTION PLEDGE**

Late last month, cancer entered the fray as Europe entered one of its periodic bouts of election fever. This time not just as an aspiration from patient groups and physicians and medical societies and researchers desperate for better prevention and care. This time it is being brandished as an election promise by one of the leading candidates for high office in the coming months. "The fight against cancer will be one of my key priorities," he said.

Manfred Weber, a German MEP who is bidding to become the president of the European Commission in November, announced what he called "his European Master Plan against Cancer"—with what he termed "a guarantee" for European citizens. This takes political lobbying over health to a new level in Europe. It gets close to saying "vote for me and I'll get you a cure for cancer"—a new twist on the familiar promises of electoral hopefuls around the world of more jobs, more money, less tax, less bureaucracy. But this pledge is very specific and is likely to be closely scrutinized. All the more so, because, at present, Weber is the favorite to win the top job in the European Union's arcane system for choosing a successor to Jean-Claude Juncker.

The plan itself is not so remarkable, covering the well-trodden ground of exploiting "innovations in the fields of biomedicine, bioinformatics, big data, and artificial intelligence," with "the patient at the center of our actions." It ticks the boxes on prevention and early detection strategies and investments in infrastructure. And it sets a goal of cure rates of "at least 90% by 2030." Difficult

to check delivery from someone standing for a five-year term of office in 2019.

Weber has also judged his pitch well to align with the currently accelerating concerns over a two-speed Europe in which patients in the former communist countries that joined the EU only in this century lag far behind the richer, older member states in the west. "Depending on the type of cancer, a patient in the east (of Europe) will have 30% less chance to heal, a dramatic and unacceptable reality. Similarly, there are fewer clinical trials currently taking place in the East compared to the West, which can make advancements more difficult to achieve." In the 13 newer member states, there are currently just under 5,000 clinical trials taking place, while in the 15 longstanding members, there are over 26,000, Weber says.

But it will be welcomed by many who have been lobbying for Europe to take a more assertive stance in health policy in general, and in cancer research in particular. They will appreciate the profile that Weber's campaign will bring with his statements that the statistics on cancer "are shocking and we must act." They will see merit in his proposal for a European Digital Cancer Center to assist clinicians, basic researchers, health authorities, and patient organizations in accessing information from health records across Europe. And they will take heart from his flourishes of military imagery: "Europe must join forces and take up arms: the fight against cancer has to be an absolute priority of the next European Commission."

Weber has enlisted support for his initiative from half-a-dozen prominent oncologists: "With a dedicated European approach,

we will be able to cure nine out of 10 children with cancer in 10 years," commented Prof. Dr. Angelika Eggert, director of pediatrics in the oncology and hematology department of the Charité Universitätsmedizin Berlin. And Thierry Philip, president of the Organization of European Cancer Institutes, said: "I found in Manfred Weber's proposal the vision, the impact, the vitalization I was looking for and as the president of an organization of 100 cancer institutes, I will strongly support it."

There is, however, a potential weakness in Weber's promise. The cancer pledge is just one of a dozen similar "guarantees" that he has issued. The others include protection of EU borders and a stop to illegal migration; the creation of a European FBI to fight terrorism and organized crime; putting an end to talks with Turkey about its accession to the EU; new approaches to rule of law; the development of smart homes for seniors; five million new jobs for our youth; cutting back outdated EU regulations; a fund financed by "internet giants" to help workers who lose their jobs to automation; home-building loans for young families; a global ban on child labor; and "an ambitious fight on climate change and global ban on single-use plastic."

The inescapable feeling is that it is election time, and candidates will say anything to get elected, including promising the moon to publics more easily won over by rhetoric than reason.

— Peter O'Donnell



## EMA NOTES

**LONG-TERM IMPLANT TO TREAT OPIOID DEPENDENCE**

In an effort to lessen opioid use disorder (OUD), the European Medicines Agency's (EMA) human medicines committee (CHMP) has recommended granting a marketing authorization in the EU for Sixmo (buprenorphine) as a replacement treatment for opi-

oid dependence. Sixmo is an implant that releases low levels of buprenorphine into the patient's body for six months. It is indicated in clinically stable adult patients who require no more than eight milligrams per day of sublingual (i.e., administered under the tongue) buprenorphine, within a framework of medical, social, and psychological treatment.

The safety and efficacy of Sixmo were studied in three pivotal trials, in 626 adult patients. One trial enrolled OUD adults who were considered clinically stable by their treating physician. The applicant is required to perform an additional study in patients in Europe to further evaluate the risks associated with the insertion and removal of the implants.

## CLINICAL RESEARCH

## A RESOURCE FOR GLOBAL RESEARCH REQUIREMENTS

The National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID) launched ClinRegs in 2014 as a free online resource for country-specific, clinical research regulatory information. Since then, the site's reach has grown extensively, with over 68,000 users from 157 countries.

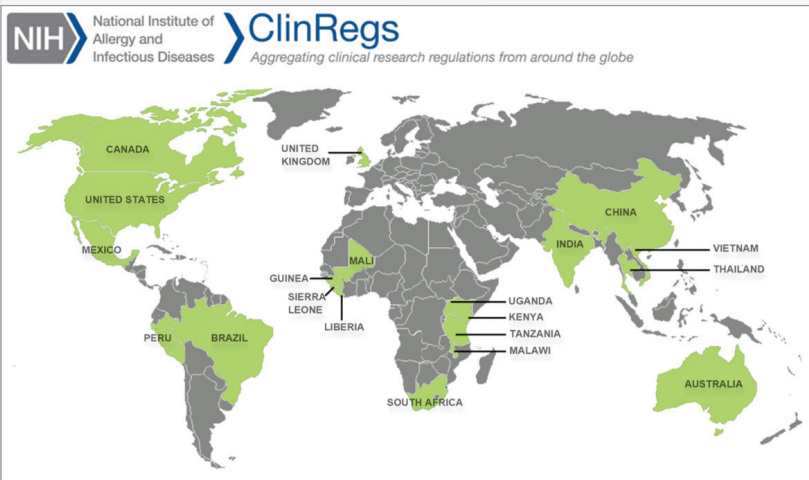
NIAID describes ClinRegs as a "time-saving resource for persons involved in planning and implementing international clinical research." The site provides up-to-date information on a wide range of specific topic areas, such as clinical trial lifecycle, regulatory authority, ethics review, informed consent, investigational products, specimens, and sponsorship.

Users can look up clinical trial requirements for 20 countries—as highlighted in green in Figure 1 at right—including Australia, Brazil, China, India, South Africa, and Thailand. The Democratic Republic of Congo is scheduled to be added later in 2019.

## Accessible and trustworthy

Key benefits for users of the ClinRegs site are the accessibility of its content and its trustworthiness. ClinRegs presents regulatory information in a way that is comprehensive and understandable, offering features such as side-by-side country comparisons. For example, when comparing South Africa and Brazil, a user would be provided with a short explanation of each country's regulatory authority and detailed information

## Trial Planning Tool



**Figure 1.** A map of countries where users can access clinical trial requirements through NIH and NIAID's ClinRegs resource.

about clinical trial application requirements and timeline. Regulations are written in plain English with a "quick facts" chart providing at-a-glance summary regulatory data at the top of each country page.

In addition to providing clear descriptions of country-specific, clinical research requirements, ClinRegs offers links to official regulatory and guidance documents. While not all documents are available in English, ClinRegs provides translations when available.

ClinRegs staff work closely with country subject matter experts who review the content for accuracy and currency. Each

section also includes the latest review date. ClinRegs users are encouraged to submit comments and suggest updates using the feedback survey and the comment tools on the site.

—Jonathan Kagan is Assistant Director, Special Projects, Division of Clinical Research, National Institute of Allergy and Infectious Diseases; Darcie Gladden is Senior Consultant at SRA International; Marie Tummarello is an Associate Data Analyst for GDIT

## REGULATORY

## SHARPLESS OUTLINES PRIORITIES AT FDA

FDA's new leader, Ned Sharpless, MD, praised the talent and diversity of the agency's staff in expressing amazement over FDA's "huge portfolio" of programs and responsibilities and emphasized that he is not planning "any radical changes" from what FDA has been trying to accomplish. This means continued efforts to support the development of new

treatments and cures and to increase competition to rein in prescription drug costs by approving more generic drugs and biosimilars. His actions will be "guided by science" and the need to protect and promote public health, he emphasized in an introductory speech to FDA staff last month.

Sharpless will seek further solutions to the opioid crisis, and he pledged support for stronger communication around the safety

and effectiveness of vaccines, citing his horror as a physician to see outbreaks of measles "making a tragic comeback because of vaccine avoidance."

His work in cancer research and treatment, he noted, has made him a "champion" of the use of real-world evidence to speed clinical trials and to support regulatory decision-making around novel products.

—Jill Wechsler



## NEWS NOTES

**J&J UNVEILS LAUNCH OF A NEW JLABS INCUBATOR**

Johnson & Johnson Innovation LLC and Children's National Health System (Children's National) announced a collaboration last month to launch JLABS @ Washington, DC, a 32,000-square foot facility to be located at the new Children's National Research and Innovation Campus in Washington, DC. This Children's National expansion is set on a nearly 12-acre portion of the former Walter Reed Army Medical Center campus in the nation's capital.

The co-location of the Research and Innovation Campus with key partners in the areas of public health research, innovation, and incubator space is critical to accelerating the translation of potential breakthrough discoveries into new treatments and technologies. The JLABS @ Washington, DC site will be open to pharmaceutical, medical device, consumer, and health technology companies that are aiming to advance the development of new drugs, medical devices, precision diagnostics and health technologies, including applications in pediatrics.

**AZ starts AI collaboration**

AstraZeneca and BenevolentAI have begun a long-term collaboration to use artificial intelligence (AI) and machine learning for the discovery and development of new treatments for chronic kidney disease (CKD) and idiopathic pulmonary fibrosis (IPF), two conditions in which the underlying disease biology is poorly understood. Scientists from the two organizations will work side-by-side to combine AstraZeneca's genomics, chemistry, and clinical data with BenevolentAI's target identification platform and biomedical knowledge graph—a network of contextualized scientific data (genes, proteins, diseases, and compounds) and the relationship between them.

Machine learning systematically analyses data to find connections between facts, and AI-based reasoning is used to extrapolate previously unknown connections. Together, the companies will interpret the results to understand the underlying mechanisms of these complex diseases and more quickly identify new potential drug targets.



An artist's rendering of the 32,000-square foot JLABS @ Washington, DC facility, set to open in 2020.

**R&D trends report released**

IQVIA Institute for Human Data Science recently released its study, "The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity." In order to examine past and future clinical trial productivity trends, the report puts forth a Clinical Development Productivity Index reflecting changes in trial complexity, success, and duration. According to the report, during the next five years, trial productivity will be heavily influenced by key trends such as including wider use of biomarkers, pre-screened patient pools, regulatory shifts, and application of artificial intelligence and predictive analytics.

For more information and to download the report, see <https://bit.ly/2Pr0SNw>.

**Caprion expands biomarker reach**

Specialty CRO laboratory Caprion Biosciences has acquired Seramatrix Corporation, a specialized provider of immune monitoring services headquartered in Carlsbad, Calif. Canadian-based Caprion plans to leverage the proprietary expertise of Seramatrix in the analysis of myeloid-derived suppressor cells (MDSC), as well as its international operations in the US, UK, Australia, and China to expand its global geographic coverage. The acquisition also reinforces Caprion's position in the provision of immune monitoring and biomarker

services to the biopharma industry to support Phase I to IV trials.

**Gilead strikes pact in NASH**

Gilead Sciences Inc. and insitro, a data-driven and machine learning-focused company, have entered into a strategic collaboration to discover and develop therapies for patients with nonalcoholic steatohepatitis (NASH). insitro's proprietary platform will be used to create disease models for NASH and discover targets that have an influence on clinical progression and regression of the disease. NASH is a chronic form of liver disease characterized by excess fat in the liver, inflammation, and liver cell damage.

**Clinerion partners with Alpha MD**

Swiss-based data technology company Clinerion is partnering with Alpha MD, a global clinical research and technology consulting firm, to expand patient treatment options in India. Indian patients may be matched with international research studies by bringing Indian healthcare organizations onto the Patient Network Explorer platform. The platform focuses on accelerating study protocol development, identifying suitable trial sites, and speeding up patient search and identification for trial enrollment.

—Staff and Wire reports

## Q&amp;A

### ONCOLOGY PHARMA DE-RISK THROUGH COLLABORATIONS, NOVEL COMBINATION TARGETS

Small biopharmaceutical enterprises face many hurdles and risks with bringing novel therapies to market. Some organizations have de-risked their approaches toward drug development by forging fruitful collaborations with medical research institutions to explore novel combination therapy mechanisms. Ahead, Spiro Rombotis, president and CEO of Cyclacel, highlights why targeting cyclin-dependent kinases and the DNA repair pathway could improve the standard of care across multiple oncology indications.

**Moe Alsumidaie:** *What is unique about the work Cyclacel is doing in cancer and what is the company hoping to accomplish?*

**Spiro Rombotis:** Our primary thrust for the last several years has been the area of cancer resistance. Genetic resistance is often observed following sublethal levels of treatment where cancer cells increase the expression of proteins that protect them and support their survival. Our goal is to try to suppress these pro-survival proteins and re-sensitize cancer cells to the effects of therapy. One of the best-known such proteins, called Bcl-2, is the target of Abbvie's Venclexta, which was approved for chronic lymphocytic leukemia and more recently acute myeloid leukemia.

Cyclacel's lead compound, CYC065, lowers the expression of a pro-survival protein called Mcl-1, which is unaffected by Venclexta. At the 2018 AACR (American Association for Cancer Research) annual meeting, we presented ground-breaking, clinical data showing a sustainable reduction of Mcl-1 for over 24 hours at tolerable levels following a single administration of CYC065. While this is excellent news, we are most excited about upcoming results from our recently initiated studies of the combination of CYC065 with Venclexta. We aim to kill resistant cancer cells by inhibiting the two pro-survival proteins at the same time, which should have a better effect over targeting just one.

Cyclacel's second thrust is in DNA repair, a field which includes patients with BRCA mutations. Cancer cells exploit the body's ability to repair damaged DNA to evade the effects of anti-cancer drugs. Cyclacel's drug candidate, sapacitabine, jams this DNA damage repair mechanism that helps cancer cells survive. After encouraging clinical data were presented at ASCO 2016, breast cancer specialists at the Dana Farber Cancer Institute conducted a study with sapacitabine in BRCA mutant breast cancer patients. Data from this study has recently been accepted for presentation at a major, peer-reviewed, medical conference later this year.

Based on this unpublished data, Dana Farber's breast cancer department has decided to run an investigator-sponsored study evaluating the effect of sapacitabine in combination with a standard-of-care drug, AstraZeneca's Lynparza in BRCA mutant, breast cancer patients. It is important to note that this is an all-oral regimen, which will help compliance in a breast cancer population where patients are typically active



Spiro Rombotis

two-thirds of cancer patients. While p53 itself is currently undruggable, it can be regulated by a family of proteins called CDKs. The benefit of targeting CDKs was highlighted by Pfizer's Ibrance, a CDK4 and CDK6 inhibitor approved in 2015, generat-

**Targeting CDK4/6 leads to a state of cell dormancy, which is initially good to stop cancer growth but can allow a cancer cell to evolve, leading to resistance.**

middle-aged women, pursuing careers and have busy family lives. We are hoping sapacitabine can improve the standard of care and lengthen the period that patients can stay on treatment.

**MA:** *For your lead cyclin-dependent Kinase (CDK) inhibitor, can you tell us more about the biological rationale for combination use in oncology? What recommendations do you have for companies that are about to test their combination regimens in oncology?*

**SR:** Our journey started over two decades ago with our founder, Prof. David Lane, who discovered p53, a gene that is mutated in

ing \$4 billion in revenue. Targeting CDK4/6 leads to a state of cell dormancy, which is initially good to stop cancer growth but can allow a cancer cell to evolve, leading to resistance.

Based on Prof. Lane's views, our rationale is to target CDK2 and CDK9 with CYC065. This leads to an apoptotic outcome or cancer cell death instead of dormancy and reduces the pool of cancer cells which can become resistant. We do not want to completely inhibit CDK2/9 because these enzymes also regulate an essential process in healthy cells called transcription. Pre-clinical tests show that transient inhibition of CDK2/9 by pulse dosing in frequent intervals



## Q&amp;A

increases exposure of the drug and induces less toxicity. This strategy aims to cause durable suppression of Mcl-1, a pro-survival protein implicated in several blood and solid cancers.

We have paired CYC065 with Venclexta because suppressing both Mcl-1 and Bcl-2 simultaneously may be more useful for patients. In 2018, MD Anderson investigators, led by Prof. William Plunkett, reported preclinical evidence that a Venclexta and CYC065 combination killed more leukemia cells taken from patients, than each drug alone. The combination was synergistically effective in killing cells with a deletion in chromosome 17p, which did not respond to either drug alone.

Our recommendations are to follow insights in disease biology, demonstrate promise in preclinical models simulating the effect of the combination, and address optimal dosing and any overlapping toxicity of the combinants as early as possible.

**MA: So, if I understand the nuances correctly, you're saying that cancer cells replicate much faster and are more vulnerable, and CDK2/9 inhibition could be able to indirectly and transiently target those cells through certain periods and stop replication. Also, this shortens the timeframe of drug exposure to limit the harm that's being done to healthy cells, correct?**

**SR:** Precisely.

**MA: How has Cyclacel been able to leverage strategic partnerships to the company's benefit? You mentioned before that you have ongoing collaborations with MD Anderson Cancer Center and Dana Farber Cancer Institute, for example.**

**SR:** We are fortunate to be working with these top-tier organizations at the fore-

front of oncology research. We believe our collaborations with academic centers of excellence are win-win, as we are offering patients in need promising therapies built on strong scientific rationale. At the same time, these collaborations help Cyclacel investigate the potential of a range of compounds simultaneously rather than sequentially, as small companies are often forced to do because of limited resources.

pacitabine in patients with incurable solid cancers. DFCI's Early Drug Development Center, headed by Dr. Geoffrey Shapiro, has been distinguished in clinical studies of novel anticancer drugs. In one study of all-comer patients with different types of cancer, Dr. Shapiro showed that breast, ovarian, and pancreatic cancers of individual patients with BRCA mutations were sensitive to sapacitabine.

These collaborations help Cyclacel investigate the potential of a range of compounds simultaneously rather than sequentially, as small companies are often forced to do because of limited resources.

The MD Anderson alliance is unusual in that they agreed to absorb almost the entire cost of four clinical programs, evaluating three of our compounds in up to 170 patients, in return for potential milestone payments upon first commercial sale in studied indications. We remain the sponsor of the studies, which means we own the data. The agreement allows us to enroll in other centers, which could expedite trial timelines.

MD Anderson's due diligence included experiments by Prof. Plunkett's group and review by senior scientific leadership alongside the business team who crafted the agreement. This is a partnership that consolidates many years of fruitful collaboration with MD Anderson investigators in various indications with multiple drugs.

Our collaboration with Dana Farber Cancer Institute (DFCI) historically involved its interest in the clinical potential of combinations of our CDK inhibitors and sa-

Data from his work published at ASCO 2016 catalyzed the interest of DFCI's breast cancer department, which is sponsoring a study to evaluate sapacitabine in combination with standard of care in patients with BRCA mutant breast cancer. One notable difference, in this case, is that while DFCI is covering clinical trial costs, they are the trial sponsor and control the protocol. We are looking forward to learning the outcome of this innovative study when it becomes available.

— Moe Alsumidaie, MBA, MSF, is a thought leader and expert in the application of business analytics toward clinical trials, and Editorial Advisory Board member for and regular contributor to *Applied Clinical Trials*

# A Roadmap for Implementing RBM and Quality Management

Mary Banach, Nimita Limaye, Steve Young, Teresa Ancukiewicz, Stephen Wilson, Johann Proeve

The importance of applying change management techniques throughout the preparation, planning, and execution of RBM and RBQM approaches.

At the 2018 DIA Annual Meeting, our DIA Clinical Data Management (CDM)/Risk-Based Monitoring (RBM) Community met with many people who were implementing or preparing to implement RBM and risk-based quality management (RBQM) approaches. Our attendees were looking for support and a forum to address their concerns. They knew that there were new guidelines and that the industry was anxious to get started with RBM activities, but they also wished to address the pitfalls one might expect. To address this need for a discussion of the changes taking place in our industry and to support each other in this endeavor, our group presented a segment of our roadmap beginning with a look at pre-study risk planning, vendor selection, and change management in RBM and RBQM.

ICH E6 (R2)<sup>1</sup> has focused upon the implementation of RBQM activities in clinical trials. Multiple stakeholders were looking for real experiences that can be incorporated into their risk management strategies. The FDA's comment period on the draft guidance "A Risk-Based Approach to Monitoring of Clinical Investigations"<sup>2</sup> reminded us of the need to focus on how we were implementing the RBM guidance. The comment period also offered us an opportunity to communicate our suggestions for how to interface with and incorporate the needs of our communities and stakeholders. Another starting point for our roadmap was the case study from Cyntegrity.<sup>3</sup> To assist in this overall endeavor, we have been working on an RBM Roadmap produced by the CDM and RBM DIA Communities. We envision a set of best practices.

## RBM—pre-study risk planning

ICH GCP E6 (R2) requires clinical trial sponsor companies to incorporate RBM in the risk management plan.

Risk planning should start with the development of the target product profile (TPP)<sup>4</sup> and then continue into the development of an individual protocol for a study. Some aspects of the TPP, such as once-daily dosing or a positive safety profile, must be taken into account when developing the risk management plan for a study.

## Risk identification

### Identifying critical data and processes

The most impactful operational risks to a prospective clinical trial will most often be associated with the most important processes. Yet, it is not only the critical data and processes, as highlighted by ICH E6 R2, but also the systems, (devices, sensors, or software apps) that are used in clinical trials that contribute to risk.<sup>5</sup>

Thus, to begin with, the study team identifies critical data, tools, and processes. One example of critical data is the survival data of patients that withdrew their informed consent or those that are lost-to-follow-up in an outcome trial. These inputs may come from data management (DM), biostatistics, or clinical operations (CO). Examples of critical processes include the timely reporting of serious adverse events to the sponsor and the adequate management of those by the sponsor. This process depends on multiple stakeholders, including DM, pharmacovigilance/drug safety, regulatory affairs (RA), medical affairs (MA), and CO. In addition, it may be worthwhile to check inspection findings from the FDA or European Medicines Agency (EMA) to see which have been areas of concern based on historic data. Keeping a closer eye on these findings may be very helpful in the future. As we will discuss later, each study team member plays a unique and crucial role in the risk-identification process. Thus, while RBM focuses on risk-based monitoring, the integration of a systemic risk management

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strategy for identifying and managing risks—from study design to the submission of the clinical study report—has resulted in a more evolved descriptor called risk-based quality management (RBQM).

### Identifying risks

Once the critical data, processes, and systems used in a trial have been identified for the study, a core study team representing cross-functional expertise should conduct an exercise of risk identification. This includes identifying all of the potential risks that may impact patient safety, data quality, and/or the operational success of the study. Identified risks should be ranked and prioritized based on three dimensions: impact, likelihood, and detectability (ILD). The product of ILD helps derive the risk score or the risk probability number (RPN). This will help the team to focus their risk mitigation efforts on the greatest risks to the study.

### Risk mitigation

Once the operational risks have been identified and characterized, the team develops a risk mitigation action plan to address the highest-priority risks. As previously mentioned, a high rate of lost-to-follow-up or discontinued patients might be an identified risk for the study. A number of mitigation actions might be considered for this risk:

1. Removing one or more ancillary procedures from the protocol requirements that are not critical to support study endpoints may reduce the relative burden on patients participating in the study.
2. Incorporate additional awareness training for sites related to this risk, including the need to check proactively with patients on their burden/comfort level with continued study participation, and what can be done to improve their experience, etc.
3. Implement one or more key risk indicator (KRI) metric to identify sites that may be experiencing a high rate of lost-to-follow-ups, missed or missing visits, or withdrawn consents.

These mitigation planning items need to be documented carefully, either within the risk management plan (RMP), risk log, or integrated quality risk management plan (IQRMP), where accountabilities can be assigned. The individuals accountable for managing the various risks must be identified via the operational plans, such as the central monitoring plan, the CDM plan, the site monitoring plan, or the pharmacovigilance plan. Thus, the RMP serves as a master plan, feeding into the individual operational plans and is, hence, described as an “integrated” risk management plan.

### Defining KRIs

Once the key risks have been specified and mitigation plans established, the complete set of KRIs to be used in support of risk detection should be confirmed. The list should ideally be comprised of therapeutic area-specific and study-specific KRIs identified during mitigation planning, along with a standard set of generic KRIs that the organization has identified to be used across studies.<sup>6</sup> The study team should identify about 10 to 25 KRIs for a study. When

the team finds lost-to-follow-up patients and withdrawn informed consent, it should monitor the KRI for an increasing number of missing or missed visits at sites throughout the study. Applying relative weights to each of the KRIs may be helpful in supporting decisions on which KRIs to follow up on as they emerge during the study and the urgency with which outliers need to be addressed. Not every risk in a study can or should be mitigated. This exercise, though, must be run very carefully in order to not overlook critical data or processes. Changes in local regulations is illustrative of a risk that needs to be accepted. It is also important that teams are trained not only on defining the KRIs, but on interpreting them as well.<sup>7</sup>

### Vendor selection for the implementation of RBM

Vendor selection when implementing RBM activities is not an easy task. It involves internal and external challenges.<sup>8</sup>

At the start, one needs to have clarity within the organization as to what are the driving factors for implementing RBM. Is this a strategic decision with clear objectives (i.e., decreased number of site visits and increased quality) and clear milestones (i.e., decreased number of site visits) that improve quality? Many companies have not bought into this model, but are merely testing the waters. Some are recognizing the significant weightage that the FDA, EMA, TransCelerate BioPharma, and the latest ICH E6R2 guidelines have given to RBM and are making tactical decisions to perform a pilot study. However, it is important to remember that the implementation of RBM involves a significant investment in technology—and the benefits of this approach may not be evident by performing one small RBM pilot study.

Implementing RBM is not just about analytics, technology, clinical, or RBM domain expertise—it is really about all of them.

Another internal challenge is whether to follow a one-stop-shop approach or to identify smaller, more cost-effective and amenable partners. There is often a lack of clarity as to whose SOPs should be followed and whose KRI libraries should be used—the vendors or the sponsors? Even more critical is the lack of pre-defined key performance indicators (KPIs).<sup>9</sup> These are essential to measure the success of the RBM implementation strategy and of the partnership as well.

A survey conducted at the 2018 DIA meeting in Boston demonstrated that around two-thirds of the participants have never been involved in RBM vendor selection, did not have internal RBM expertise, and had not defined KPIs for RBM implementation within their organizations. This shows us the challenges that the industry is facing today.

Implementing RBM is not just about analytics, technology, clinical, or RBM domain expertise—it is really about all of them. Finding a vendor who really understands the science of RBM is important. It is cru-

cial to work with a vendor who not only has a lot of experience, but is also willing to share its learnings with the sponsor company. A vendor (CRO) may have significant clinical trial experience but does not have a rich RBM implementation experience. This needs to be validated carefully. Alignment in terms of scale and geographical footprint is also important when establishing a preferred partnership. Does the vendor actually have RBM capabilities at the required locations?

Perhaps even more important than all of the above is the cultural fit, the alignment in vision, and the flexibility and transparency offered by the vendor. This would go a long way in terms of transforming this from a sponsor-vendor relationship to a true partnership.

### Principles of change management applied to RBQM

Why do we need to address change management as part of RBQM preparation? What do we mean by change management? John Kotter, the guru of change management, refers to the eight stages that are required for the transformation and change to take place.<sup>9</sup>

1. Establishing a sense of urgency
2. Forming a powerful guiding coalition
3. Creating a vision
4. Communicating the vision
5. Empowering others to act on the vision
6. Planning for and creating short-term wins
7. Consolidating improvements and producing still more changes
8. Institutionalizing new approaches

Change management, in the context of instituting RBM and RBQM practices, refers to more than just the relationship between the sponsors and the sites. In following the stages listed above and implementing a vision, one needs to integrate a change management strategy from the risk identification stage itself and through the entire risk management planning and vendor selection stages, as well as developing a cohesive RBQM plan, addressing the needs of each stakeholder.

Consider changes within the organizations and how they are affected by RBQM. Successful change management for the adoption of RBQM is much bigger than our relationship with the sites. It speaks to changes in our relationship and understanding of all of the clinical trial processes and study data. It speaks to transformations in how we conduct clinical trials and how we, as a community, work together and support each other. The new RBM approach is not a competition between stakeholders, but rather a way to assist each other in minimizing risk and enhancing the quality of the output of all stakeholders.

Bottom line—change management and the adoption of RBQM means disruption. RBQM offers a disruption that will improve the organization.

How do we differentiate resistance versus misunderstanding? How do we address those who see the benefits but are lacking in a commitment to the rigors required of change? Do we have time to make all the changes that are necessary? How do we prepare everyone for the bumpy first pass?

As we have seen in implementing RBQM best practices, we are involved in actualizing all eight stages at the same time. We are often not in a position to build a powerful guiding coalition before implementing the changes. Yet, the implementation of all eight stages is required for success. There is no option to not implement RBQM. How can we use Kotter's stages to help us in our preparation and planning?

#### 1-Establishing a sense of urgency

Pharma is experiencing a sense of urgency for adopting the principles of RBQM. For DM preparing internally for the adoption of RBQM, questions about systems, case report form (CRF) designs, and the timeliness of implementation lend all data activities a sense of urgency. Clinical operations teams express a sense of urgency regarding training and education on the new terms and processes. For regulatory, quality, and program managers, the sense of urgency is two-fold: first, assessing preparedness for RBQM, and, second, demonstrating preparedness. This is equally important for quality assurance (QA), as QA needs to ensure that all SOPs are in place, teams are trained on the same, and training records are in place as well.

Change management, in the context of instituting RBM and RBQM practices, refers to more than just the relationship between the sponsors and the sites.

#### 2-Forming a powerful guiding coalition

It is not only the leader who is in charge of developing the KRIs, but rather a coalition or a group that can work together. Many leaders look forward to building a guiding coalition in implementing RBQM. Who has the right skills for taking the lead? Who is writing the SOP?

Monitors often fear that they have become dispensable. They fear that communication with the site will be centralized and personal interactions will disappear. They also fear that data managers may not understand how much the sites might skew the data. For regulatory, quality, and program managers, a guiding coalition of leaders is essential. Their underlying fear is that they will not be seen as an important voice in the leadership program. The main fear is disruption and loss of quality due to the new process.

The vendor's experience in change management is worth assessing. Both the sponsor and the vendor need to join hands in the implementation of a strategic change management approach within the sponsor's organization, and attempt to address the concerns of naysayers.

#### 3-Creating a vision

Creating a vision for the implementation of RBM and RBQM depends on a succinct determination of what are considered to be best practices within the organization. With many participants offering their visions, the essential elements can be obscured or may, at times, ap-

pear too discordant to be put into practice. As discussed earlier, it is a shared vision that brings the team together.

For the data manager, a clear vision entails updating and executing new systems for RBQM. Who is doing the testing? When does one have time for testing? How are deviations from critical data points identified, interpreted, and actioned? For monitors, there may be conflicting visions. Some individuals may not see the changes as beneficial. Changes in visit schedules and data points to be reviewed can be disruptive. RBQM may feel too open-ended—how does one check for deviations and ensure quality at the site remotely? How does one retrain the site when difficulties are noted?

RBM results in a disruptive change, not only in monitoring methodology but also in organizational structures and processes, which is not an easy thing to accept. It is important that the sponsor recognizes the commitment that these changes will require. How does its vision for RBQM answer the requirements of the regulatory authorities as well as address the institutional procedures?

#### 4-Communicating the vision

In communicating the vision, we need to show value. What is the value that RBM and RBQM will bring to our organization? It is important to let everyone know what is being planned and to address all concerns. Concerns vary in nature for different stakeholders. Data managers may have concerns regarding who is going to define the KRIs and how they will be collected in the study. Monitors may be concerned about what they should be communicating to the site and whether the site will buy into that message. RA may have its own perspective regarding whether RBQM will really add value, or will it just pose one more regulatory hurdle? Sites are often not even informed about the change in approach, despite being the most important stakeholders after the subjects. Technology teams may have concerns around whether their platform solution will pass muster with the end users (the central monitors) and with auditors.

An organization must have internal RBM experts (or utilize external consultants) to be able to make meaningful, well-informed decisions. A lack of internal champions may often set this up for failure.

#### 5-Empowering others to act on the vision

All stakeholders within the company and externally should be empowered to follow and contribute to the vision. As the key in the structure of implementing RBM and RBQM in the institution, central monitors are connected to all parties within and outside the company. A clear message on the implementation strategy and how structures are changing will empower everyone that is impacted by RBQM.

The DIA survey revealed that 40% of the participants found the lack of internal champions to be the biggest challenge within their organization, followed by a lack of vision.

#### 6-Planning for and creating short-term wins

It is good to demonstrate success early on to show where the organization is headed and what can be accomplished. Again, showing value is essential in creating short-term wins.

The RBQM approach is integrated right from the start of the

study.<sup>6,10</sup> Central monitors can show how well it's worked by identifying outliers in critical data points, and alerting monitors to take corrective action. The monitors can demonstrate short-term wins by addressing these issues remotely and actually enhance the quality of the data being received from the site. Sites that are doing well, despite fewer visits, should be recognized for their achievements. For sites that need more frequent visits, the win can be to demonstrate early identification of issues and ease of follow-up.

**The secret to success for implementing change management includes transparency and the consistent ongoing communication of a shared vision.**

#### 7-Consolidating improvements and producing still more changes

Once one has a short-term win, it needs to keep the momentum in place for the next set of changes. This requires preparation and planning. The first short-term wins are great, but consolidating these improvements requires vigilance. One may not have all the answers to the problems and challenges along the way. For example, a KRI that is cumulative may not be sensitive enough to show us how the site is improving or worsening, but it gives us an opportunity to consolidate our improvements and produce more changes.

#### 8-Institutionalizing new approaches

The final reminder in any change management plan is that change takes time. If one rushes through the process without validating that everything is done, it is likely that the program, in turn, will suffer. We have often seen that starting and then stopping the implementation and going back to the old ways can be more harmful than waiting until everyone is prepared to get started.

Although companies that transition an ongoing study to the RBM approach may find it more challenging than starting with an RBM approach from the beginning, it is not impossible. But it's crucial to get started with RBM the sooner the better.

Institutionalizing these new approaches always takes time. The secret to success for implementing change management includes transparency and the consistent ongoing communication of a shared vision.

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# Work Planning & Approaches to Overcome Bottlenecks

Christian Rack

Outlining a resource planning and scheduling model, using the example of an analytical department in drug development.

Each department, from production to clinical research, deals with three types of work: maintenance, routine, and project work. The work shares vary with the nature of the work, but all departments have to balance out the workload against the capacities. In this system, it comes to goal conflicts when the workload exceeds the capacities for the considered period.

The aim of the article is to provide a resource planning and scheduling model, using the example of an analytical development department that includes the special characteristics of chemical analytical tasks in an R&D environment.

## Planning of the analytical lab

Analytical chemistry is needed during all phases of developing a new drug product.<sup>1</sup> More than 50% of the chemistry, manufacturing, and control (CMC) section of a dossier can be attributed to chemical analysis services, which include the development and validation of methods for raw materials and the drug product, the characterization of reference substances, the examination of container closure drug product interaction, and the development of stability indicating methods and execution of stability studies. However, analytical tasks are often on a critical path.<sup>2</sup> Therefore, they gain a lot of attention, often combined with the desire to speed them up. This need is directly related to topics like resources, priorities, and all activities that might lead to faster results. At the core of those discussions is often a robust and defensible planning system that tries to solve goal conflicts by checking priorities and allocating resources.<sup>3</sup>

Planning is a process needed to evaluate how many and what resources are needed to perform a job, considering the given time and priority. One of the biggest challenges in an analytical laboratory in an R&D environ-

ment is variable demand, resulting in an uneven workload combined with numerous tasks.<sup>3,4</sup>

These requirements demand different types of planning levels and scheduling to create a robust framework (see Table 1 on page 18).

## Resource planning

The available resources can be calculated as follows:

$$h_{total} = h \times 52 - (ho + lho + do)$$

- $h_{total}$  = available hours per person per year
- $h$  = weekly working hours
- $ho$  = holidays
- $lho$  = legal holidays
- $do$  = average days off because of illness

Extra hours might be considered, depending on the company culture and work contracts.

The available resources are normally used for:

- 1.) Development projects
- 2.) Standard tasks
- 3.) Maintenance
- 4.) Special tasks or other unforeseen projects

The time used for development projects can be separated in straight analytical topics, for example, method validation, or in topics where analytical service is needed from other development departments.

Standard tasks need to be planned for periodically recurring samples, such as stability measurements. Those tasks are characterized by regularly scheduled samples and an even workload, but mostly without flexibility. For example, a stability test must be performed in a short period of time after removal from the climate chambers.

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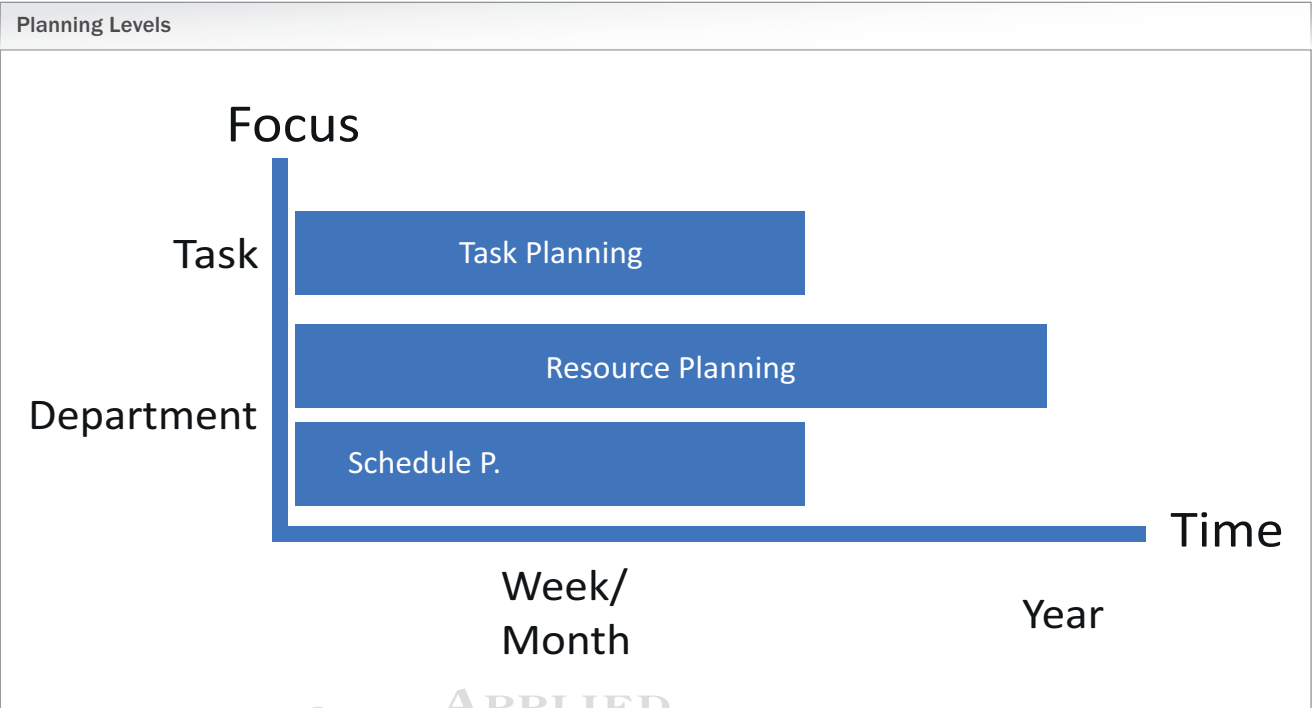
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Source: Rack

**Table 1.** The difference between resource, schedule, and task planning is based on the considered period and the focus.

The maintenance time is relative to the type of equipment and to the number of people. The time needed to do the requalification or calibration work is related to the number and type of analytical equipment. The time needed for training (practical, theoretical, external, internal, doing training, receiving training), SOP reading (technical, good manufacturing practice [GMP]), and administrative work (lab journal) is related to the number of people. This time requires, in most cases, an absolute number of hours, which is in percentages higher for part-time employees (leading to the fact that two part-time employees do not have the same output as one full-time employee).

In conclusion, the more diverse the equipment and the higher the GMP requirements (as a result of the development phase), the higher the maintenance rate.

Special tasks could come to the R&D lab if the special expertise or the equipment of the R&D lab is needed, for example in cases of troubleshooting. Unforeseen tasks could come from projects if, for example, a health authority needs additional data or if experiments fail. The samples coming from these types of tasks are unplanned. For those tasks, a buffer time should be planned. This buffer allows to react on those incidences without completely rescheduling the whole planning.

The resource planning should be repeated at regular intervals based on the dynamics of the forecast. Yearly and quarterly or monthly could be typical intervals.

**Schedule planning**

The schedule planning has one macro point of view and one micro point of view.

The macro point of view considers that some tasks have to be executed in a certain order. For example, before you can validate a method, you must have a developed method, and the needed reference substance must be available. There are dependencies or typical sequences of activities that every lab has and that must be considered for the planning.

The micro point of planning affects the task. To perform a certain task, the following prerequisites must be in place:

- Skilled analyst, which means: GMP trained, trained on the method and/or equipment
- Available equipment, which means: qualified status, suitable for the requirements

The schedule planning is repeated on a daily or weekly basis based on the dynamics of the lab. Due to equipment shutdowns or illnesses, it is necessary to react on short notice.

**Task planning**

There are some metrics that are interesting in every lab. Those are:

- Time needed to perform the analysis
- Duration from the order to the final, approved result
- Number of analyses performed in a given timeframe

Obviously, there is a difference between analysis time and the overall length of a task. If you break a task down to all the details, you realize that even one task could take up to 30 single steps, (e.g., plan

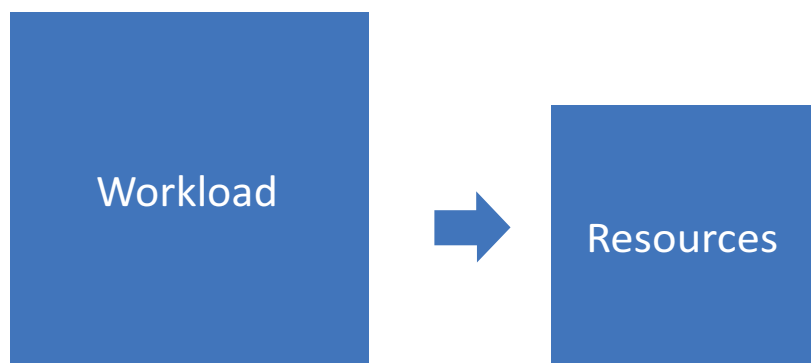
creation, internal review, approval loop, review by QM, training of the plan, etc.).

Task planning deals mostly with synchronizing the different departments and people and their tasks on the interfaces. Planning should be initiated by a kickoff. Further meetings should take place depending on the number of interfaces.

The number of analyses in a certain time-frame is influenced by the following aspects:

- Batching of tasks: Can samples be collected and analyzed in a row?
- High frequency vs. low frequency tasks: Are reagents in place; are forms created?
- How is the proficiency of the technician on the type of method?

#### Uneven Distribution



Source: Rack

**Figure 1.** The workload is higher than the available resources for the period considered.

### Overcoming bottlenecks

Since the creation of analytical results or analytical methods is normally the last step of a task or a project, any delays get high attention. This attention normally correlates with the willingness to speed up the process. Dependent on where the bottleneck occurs, different approaches could solve the problem.

### Overall resource problem

In case the resource planning shows that the workload is higher than the available resources (see Figure 1), the following general options are possible:

- 1.) Increase resources
  - a. New staff from external
  - b. New staff from internal departments
  - c. Outsourcing of activities to external
  - d. Outsourcing of activities to internal departments
- 2.) Reduce workload
  - a. Prioritization
- 3.) Move resources
  - a. Value stream map

One of the first ideas to overcome resource problems is to hire new staff. While this is the most powerful option to increase resources long term, it should be carefully evaluated as a short-term option. The more complex the role of the staff is, the more training is needed until a person could help. In this time period, resources are taken from the available staff to train this person. The amount is reduced if you hire an experienced person, but time is still needed. One option that works on short hand is to remove the low brain work from the available staff and hire someone for this type of work (e.g., cleaning of glass ware).

The mentioned considerations also apply for new staff from other internal departments. However, the significant benefit here is that the

overall training for software, systems, etc. is not required anymore.

The same problem applies for outsourcing. The outsourcing of any activities requires further activities. Depending on the project stage, method transfer activities are needed. Furthermore, an external lab needs an internal counterpart for questions. The time needed for the handling of the external laboratory should always be included in the calculation.

The mentioned considerations also apply for moving tasks to other internal departments that require ongoing support.

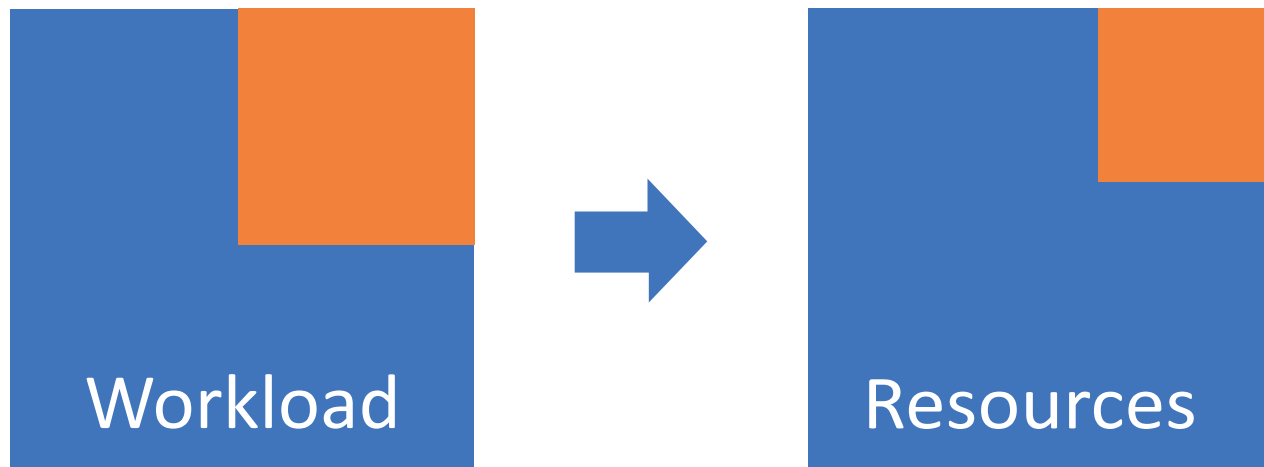
The next option is to reduce the workload by a clear prioritization of the work. While this point sounds simplistic, in reality, there are some hurdles. The first hurdle is that the lab needs transparency about all tasks and the estimated hours to fulfil those tasks. This includes the internal tasks for maintenance. The next hurdle is that a lab normally has different internal customers with their own priorities. Creating an overall priority list is normally not possible, because a prerequisite would be that all internal customers are aligned. To solve this issue, the best option is to allocate different resources for the different customers, (e.g., 20% for QC, 20% Life Cycle Projects, 60% R&D Projects). Within each section, it is much easier to set priorities from A-Z.

Another option that is quite normal in production departments, but less common in R&D departments, is to create a value stream along a standard development project. According to a short benchmark study, the common ratio of formulation development to analytical development is 1:2, excluding any activities for life cycle management and direct support of the QC and production department but including the management of external resources for special analytics. If the stability studies are outsourced at an early stage, a ratio of 1:1,<sup>5</sup> could be sufficient, but it should be not less. However, if the ratio between the development departments is not harmonized, there will be always one department waiting for the other.

### Temporary resource problem

In the case that bottlenecks occur during the schedule planning (see Figure 2 on page 20), the following options are possible:

## Specific Work Bottlenecks



Source: Rack

**Figure 2.** Overall workload equals available resources, but for a certain type of work (symbolized by the orange square), the workload is higher than the available resources for the period considered.

- 1.) Equipment related
  - a. New or better equipment
- 2.) Staff related
  - a. Cross qualification
  - b. Leaner qualification/training
  - c. Moving maintenance
- 3.) Planning related
  - a. Lowering the number of unmovable tasks
  - b. Installing KPI

If there are bottlenecks due to limited analytical resources, new equipment or improvement of the current equipment would solve this issue. New equipment leads to qualification efforts, which might include training of the technician in the short term and higher maintenance level in the long term. However, if there is a long-term demand for new equipment, due to a new product class or the introduction in the pharmacopoeia, this step could solve this issue.

Sometimes, there is a resource problem for a special analytical method or an analytical instrument, because not enough staff is trained for this method or instrument. To overcome these training limitations, it is self-evident to cross-qualify all staff members of a laboratory. The ideal lab technician is one who is capable of performing all sample preparation steps and who is skilled to use all analytical instruments. In reality, however, this is limited by the following two points:

- A lab technician, who is focused only on a limited number of analyses, is familiar with a method or an instrument, which results in an increased speed and higher output.
- A lab technician, who is trained on a new method or a

new equipment, needs to use his skills at least every three months to maintain this newly acquired skill. This must be considered if there is a decision to train an additional technician for seldom-used analytical techniques.

A leaner qualification or training program is something that should be discussed with the training department. An aspect is that most training departments are located in quality departments. Accordingly, the training programs are focused on showing GMP compliance to the auditor. The training programs are often not designed to minimize the on-boarding time.

**Having a high number of unmovable tasks lowers the flexibility to react on unforeseen tasks coming from deviations or other unplanned activities.**

Moving maintenance activities for equipment leads to a blocked equipment status. But, in case a certain equipment is not needed in a given timeframe, this approach would transfer working hours from the timeframe into the current timeframe (dependent on the requalification frequency).

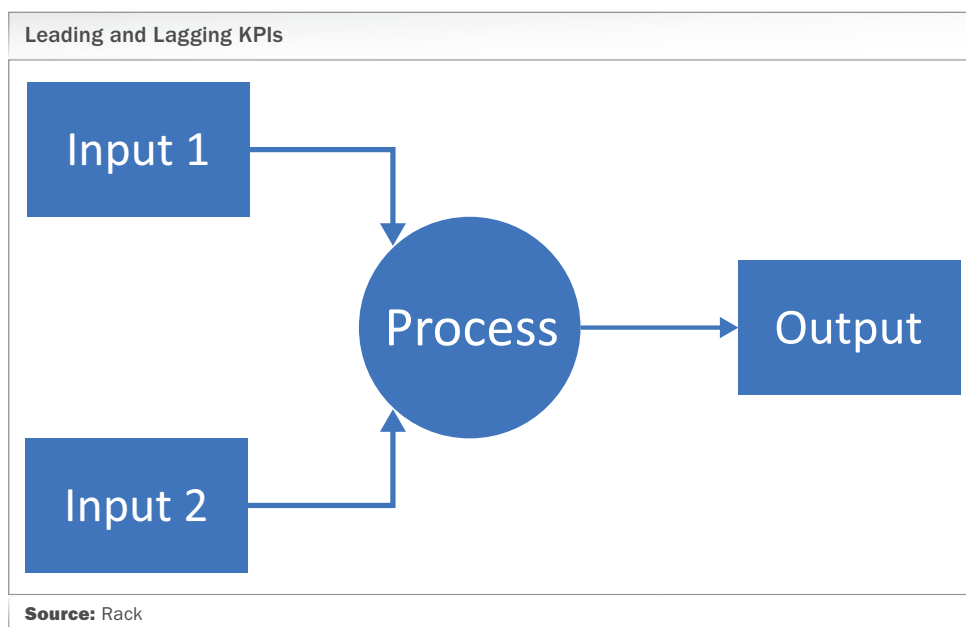
Another aspect that limits the flexibility of the analytical laboratory is the percentage of unmovable tasks. Unmovable tasks are usually:

- Execution of stability studies
- Support of investigations during a deviation

- Support of the QC department with analysis needed for the batch release
- Development tasks due to deficiency letters with strict timelines (e.g., clock stop)

Having a high number of unmovable tasks lowers the flexibility to react on unforeseen tasks coming from deviations or other unplanned activities. The higher the percentage of already-blocked hours, the higher the impact that unforeseen activities have. This could be anticipated by blocking a certain percentage (e.g., 10%) for unplanned activities.

There are two types of key performance indicators (KPIs), leading and lagging KPIs (see Figure 3). While the lagging KPIs are normally of interest to the internal customers, it is recommended that the analytical lab also tracks leading KPIs that have an influence on the lagging KPIs. Recommended is a KPI like "hours for unplanned tasks, requested in the last month." This KPI forces everyone to think about priorities. Assuming that an unforeseen task could be analyzed along the way, without having an impact on the other work packages, it is an illusion.



Source: Rack

**Figure 3.** Lagging indicators (Output) measure the outcomes of what already happened; leading indicators (Input 1 and 2) provide information that may predict future outcomes.

of the aforementioned steps could help to identify approaches to overcome bottlenecks.

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Care, B. Braun Melsungen AG

## Task-related problems

These problems normally show up as unwanted waiting time. The following option is possible to overcome those bottlenecks:

- Installation of a task (project-) owner in the analytical lab.  
A standard analytical task, for example, a method validation, could consist of several small steps, as mentioned earlier. In case several persons are involved, and time is critical, it is recommended to install a task owner, who is the single point of contact for all persons to report delays and synchronize all activities.

## Conclusion

Finding the right balance between planning and over-planning is often a difficult extremum problem. On one hand, it is an illusion that 100% robust planning can be achieved in a non-linear and highly dynamic system like an analytical development department.

On the other hand, the number of different tasks and their dependence on each other is so complex that planning is needed to avoid waiting time. The other important aspect of planning is that it generates a transparency that is highly needed when it comes to justification of resources and overcoming goal conflicts.

In conclusion, planning of the analytical laboratory remains one of the most complex tasks in resource planning, but the consideration

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# Relying on Data and Behavior Science to Unlock Real Change



What small “nudges” can serve as reminders and relevant motivators to help patients meet their goals, talk to a physician, explore a clinical trial, or stick with a treatment?

## Michelle Keefe

President of Commercial Solutions, Syneos Health

“Proceed boldly” is a common mantra within industries experiencing intense market pressures. But is it suited to the life sciences? Can pharmaceutical companies embrace unfamiliar approaches, replace their decades-old traditions, and view their stakeholders through a new lens? Experience suggests that new directions are possible for companies that make use of data to focus their resources and of behavioral science to understand their stakeholders.

A recent study by *Managed Healthcare Executive* found that leveraging clinical data and analytics is one of the biggest challenges that healthcare leaders face. Typically, they have issues with managing large data sets, working across data silos, and extracting data that’s meaningful to different stakeholder segments. Meanwhile, studies have shown a direct correlation between an organization’s “data literacy,” or the ability to turn data into meaningful information, and its financial performance.<sup>1</sup>

The fundamental step in making data more actionable is to systematize one’s approach to it.

Not all data are necessary; it’s a matter of turning to just the right data. Often, the most useful data sets for providing clarity in healthcare decision making aren’t from large, legacy, proprietary sources. Frequently they’re from quickly accessible—and sometimes even open—sources.

The right data can answer questions of “who,” “where,” and “when,” revealing which patients might benefit most from a treatment, where those patients can be found, and when in their treatment journey a treatment will be most helpful and successful. Such information can be used to direct resources in both clinical and commercial operations.

Data, however, cannot answer “how” questions such as: how can we connect with people and motivate them despite the noise, doubt, and fear present when they are ill? For that, we must turn to behavioral science. Behavioral science explains why people do what they do and which personal levers can activate or change their behaviors. What small “nudges” can serve as reminders and relevant motivators to help patients meet their goals, talk to a physician, explore a clinical trial, or stick with a treatment?

Research conducted by Strava, the social network for athletes, found that most people fail to

keep their New Year’s resolutions by January 12th. Imagine if patients only adhered to their treatment regimen for 12 days. Patients often need help to complete a complex, critical healthcare journey. They may need support and motivation to try and try again when they face a barrier or simply miss a treatment. Just as clinical data leads to precision medicine, behavioral science leads to precision interventions.

Life science leaders are managing pressure on time and resources at a moment when the velocity of change and opportunity is faster than ever. Companies are entering new markets, engaging new customers, and leveraging new technologies. They need to validate unfamiliar approaches and drive change.

Many healthcare leaders are struggling with gaining strategic traction around that transformation. They understand they should be doing things in bold new ways, but the clarity around how isn’t always there. Organizations can only transform when they have data-driven proof of where to focus and an incredibly deep understanding of the stakeholders.

As an industry, we need to take the next step beyond “explaining” and “predicting” customer behavior, we need to employ evidence-based strategies to change it by helping customers make well-informed decisions and follow through on their intentions. The insight derived from combining data for focus and behavioral science for relevance has the potential to change the industry, as well as patients’ lives.

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