APPLIED
CLINICAL TRIALS

OCTOBER / NOVEMBER 2016

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT

Volume 25 Number 10/11 October/November 2016

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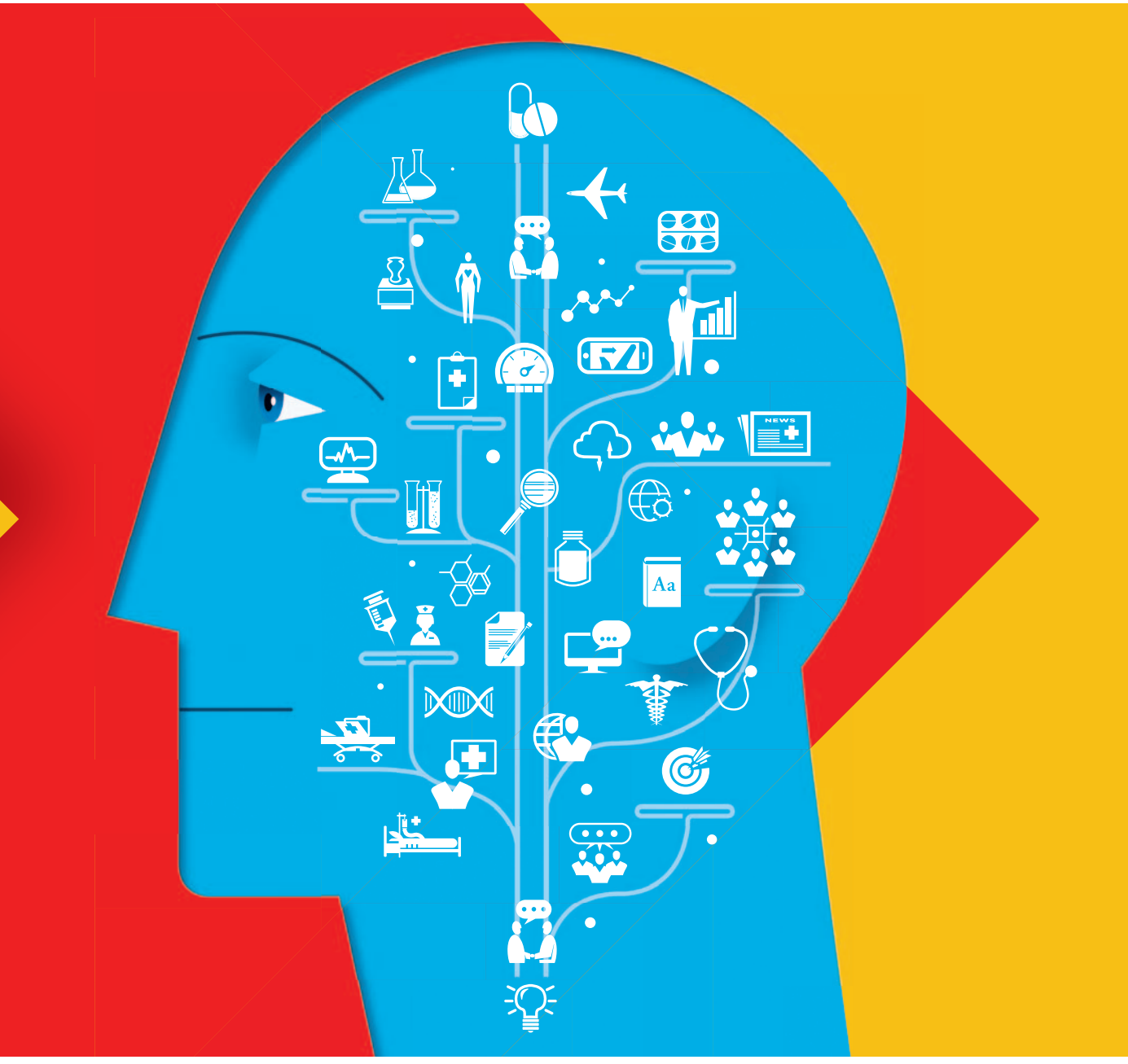

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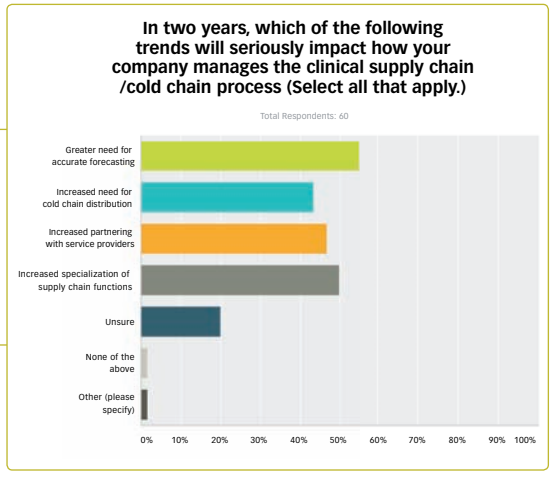
Trends That Will Impact the Clinical Supply Chain



Source: *Applied Clinical Trials*, SCORR Marketing Survey, July 2016. http://bit.ly/2d8LaHI

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Innovation Survey

Did you miss the results from our latest joint survey with SCORR Marketing? ***Innovations in Clinical Trials*** examined attitudes toward implementation, stakeholders most accepting or resistant to innovation, the potential areas of benefit and more. Download here: http://bit.ly/2ckpQcd

CFDA Update

Strengthening communications between applicants and CFDA's CDE

In June, the China Food and Drug Administration (CFDA) promulgated a regulation to streamline the drug development and technical review communication between the agency's Center for Drug Evaluation (CDE) and the applicant. The CFDA adopted communication procedures similar to those used in the U.S., with some small differences. Previously, the application channel for the communication meeting between the CDE and the applicant was not clear; only meetings for drugs under special review were commonly approved. With this new regulation, it is easier for applicants to get the opinions of CDE reviewers to guide their drug research and development processes.

Shortening the application timeline

Multiple measures have been taken by the CFDA to resolve the backlog of registration applications. The agency is trying to clear the backlog inventory before the end of 2016 and is attempting to meet the regulation-specified timelines in 2018. Since the CFDA increased the drug registration fee significantly, the CDE has been recruiting more technical reviewers to resolve the resources issue. The number of CDE reviewers is expected to reach 500 by the end of the year, up from only around 100 in early 2015.

Visit http://bit.ly/2csNTZ5 for the full version of this article

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VIEW FROM BRUSSELS

Health Technology Assessment: Europe Peers Into the Mist

Clarity sought on HTA's role in clinical trials

Everyone agrees that there should be more health technology assessment (HTA). That's the easy part. The real challenge is defining what sort of HTA, and how it should overlap with other elements of the decision-making chain—including with clinical trials. And that is where Europe is at present trying to look ahead and seek some sort of consensus. But it's a tough-ask anywhere in the world—and in Europe it is, as usual, even tougher, because it means getting agreement among dozens of countries that each has its own views. In the EU there are more than 50 national and regional HTA bodies, all embedded in different institutional settings.

That is why the European Commission has just published what it calls an inception impact assessment on strengthening EU cooperation on HTA. Cooperation is perceived as an effective way of maximizing the use of resources—and making efficiency gains that can palliate the remorseless rise in spending occasioned by Europe's ageing population, the increased incidence of chronic disease and the cost of complex new technologies.

The scope of the reflection is broad: drugs, devices and medical, surgical and radiation procedures, and also measures for disease prevention, diagnosis or treatment. And it takes account of both approaches to HTA—the rapid relative effectiveness assessments (REA) that cover clinical domains and measure the medical/therapeutic added value of a technology, and the full assessments that also include cost-effectiveness, budget impact, ethical, legal considerations, and impact on patients or the organization of healthcare systems.

In exploring possibilities for closer cooperation, the EU is between the rock of respecting diverse national approaches and the hard place of tackling budgetary constraints on healthcare. There is no doubt about the budgetary constraints. But there are plenty of questions over the different approaches. In the last 20 years, most member states have introduced their own HTA systems at national or regional level, and they differ widely in procedures and methodologies—in everything from data requirements for the submission dossier to the choice of comparator, and the way in which the added therapeutic value is expressed. While clinical trial data is a core requirement for all agencies, industry indicates that differences exist in the type of trials requested. Safety data, quality of life data and economic analyses are commonly requested, but not by all HTA bodies. Real-world evidence and additional studies may also be required.

Diverging methodologies lead to diverging outcomes, so informal attempts to get them to work more closely together have been underway for a decade. And since 2013, health ministries or national HTA authorities have met regularly—although on a voluntary and non-binding basis—in the framework of an HTA network. The network has been supported by a series of short-term programs to boost scientific and technical cooperation. These so-called joint actions have focused on developing common methodologies, on piloting joint REA and full HTA reports and on developing and maintaining common IT tools.

Outputs of the joint work so far include some standardized framework for HTA assessments, related methodologies and tools covering clinical and non-clinical elements, literature reviews and early dialogues and scientific advice on development planning and study design. There has also been some move toward supporting member states in providing objective, reliable, timely, transparent, comparable and transferable information, and easing information exchange. The cooperation led to the production of about 20 joint reports, including REA and full HTA, and some 20 early dialogues between technology developers and HTA bodies, which help industry to design the studies in terms of regulatory and HTA requirements.

The latest of these joint actions has just started, and will run until 2020. It involves 75 partners from 29 countries, and it plans to generate 80 joint reports and 35 early dialogues, as well as increased uptake of the joint work at national level. It will also review current guidelines, models, methodologies and tools, and develop new ones, to promote continued HTA collaboration at the EU level beyond the end of the project in 2020.

However, despite the developments in joint work over recent years, national authorities still carry out their own national assessments, because the scheme is entirely voluntary, and national uptake remains at the discretion of each member state. So they can—and do—choose to ignore all the joint work, and the intended cooperation is further impeded by legal, organizational and even linguis-

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tic barriers. As a result, uptake has been the exception rather than the rule.

When the costs of HTA are taken into account, the consequent duplication doesn't come cheap: each national HTA assessment is estimated to cost around $30,000 to national bodies and $100,000 to the industry. And these figures are only for REAs (they need to be more than doubled when full HTAs are undertaken), and they do not include the expenditures of collecting additional data to meet the differing requirements of national HTA bodies.

Over the last two years, EU ministers have repeatedly acknowledged the importance of HTA and called for continued support for cooperation, with reinforced attention to its use in the context of personalized medicine. The European Parliament has echoed the calls, and the HTA network itself has urged support for joint work over the long-term.

The Commission, too, has pointed to the "very high" fragmentation of HTA systems in the EU, and identified the lack of "binding mechanisms for mutual recognition of joint assessments" as one of the major shortcomings of the current HTA system. Patients, health professionals and public health organizations have added their voices to the calls for strengthened HTA coordination at the EU level, to avoid unnecessary duplications of efforts and promote evidence based health policies.

So, too, has the pharmaceutical industry, which seeks consistency of the data requirements and clinical assessments, although with some reservations over full HTA at the EU level. Health insurers and other payers also want to be involved in HTA cooperation, particularly so that requirements on clinical evidence and cost-effectiveness of technologies can be aligned. And at the international level, the World Health Organization has urged its members to develop and apply HTA and to strengthen inter-country collaboration to obtain efficiencies.

The Commission is now seeking views on whether it should continue to fund the efforts to promote cooperation and convergence after the current program runs out in 2020. Without EU funding beyond 2020, the current cooperation will not continue or will be very limited, it believes, and the achievements of the cooperation to date—on common tools, methodologies and joint assessments—are at risk. But the Commission suggests that longer-term funding rather than a further series of five-year programs might be more effective in ensuring voluntary cooperation.

Another option under consideration is moving beyond purely voluntary cooperation, and introducing a legal framework for HTA cooperation. This could provide a mechanism to ensure that the efforts of national bodies in collecting data were compatible, shared and used, and allow for the production of joint REA reports. In a still greater shift toward legally binding cooperation, member states might not only jointly produce REAs, but could be obliged to use them. And an even greater level of mandatory engagement could see joint production of full HTA reports—covering economic, ethical, legal and organizational issues, too.

Don't hold your breath in the hope that this will provide all the answers either. The document frankly admits that "no comprehensive analysis of the impact of HTA on resources has been concluded thus far." To add to the confusion, the Commission states boldly: "This inception impact assessment is provided for information purposes only and can be subject to change. It does not prejudge the final decision of the Commission on whether this initiative will be pursued or on its final content and structure." The only thing that can clearly be seen in the HTA mist at present is the mist.

VIEW FROM WASHINGTON

PDUFA VI Promotes Patient Views, Innovative Trials

FDA officials and industry leaders have agreed on a set of recommendations for revising and updating the Prescription Drug User Fee Act, with an emphasis on including patient views more systematically into the process for evaluating and vetting innovative therapies. A main theme of the PDUFA VI "commitment letter" is to support development of breakthrough therapies and treatments for rare diseases by conducting public workshops that lead to guidances on collecting patient input on disease burden, treatment impact and clinical outcomes assessments most important to patients (see http://bit.ly/29ARF3j).

This emphasis on hearing the patient voice also aims to encourage innovative clinical trial designs. The program calls for advancing clinical trial simulation approaches and to expand use of adaptive, Bayesian and other novel trial designs to support model-informed drug development approaches.

A related initiative is to make greater use of real-world evidence (RWE) in evaluating efficacy during the approval process, as well as in tracking safety issues postapproval. PDUFA VI expands FDA's Sentinel system for monitoring drug safety and emphasizes the need to update benefit-risk assessment in drug development and postmarket evaluation.

Improved FDA oversight of combination products is another new goal. The program calls for expanding staff and promoting more coordination between the Office of Combination Products and review centers for drugs, biologics and medical devices. Fee revenues will support additional reviewers for these complex products, development of guidances on bridging studies and labeling, clarification of protocols for human factors studies and an independent outside evaluation of the combination program.

New fees, operations

These and other initiatives will be supported by a significantly revised PDUFA fee structure that sponsors and FDA officials hope will make payments more predictable for all parties and create a more sustainable and manageable program. The current $2 million-plus fee for filing an NDA or BLA may drop somewhat, as a new "program" fee provides more of PDUFA revenues. This fee replaces current levies on manufacturing facilities and products and will be based on the number of approved drugs and biotech therapies marketed by a firm. Program fees will be calculated to yield 80% of the anticipated $1.2 billion collected by PDUFA in 2018, while application fees will support only 20% of program costs, thus reducing FDA's reliance on revenues that can vary from year to year. But to avoid discouraging development of personalized therapies that may have five, 10 or more different formulations of the same product, a sponsor will have to pay the program fee for a maximum of five versions of the same drug.

Another notable change is to drop user fees altogether for efficacy and manufacturing supplements. The new policy doesn't reduce FDA fee revenues that much and could prompt sponsors to update labeling more often and more quickly. The revised fee program also encourages manufacturers to submit full information on the facilities where a new therapy will be produced by stipulating that an approval goal date can be delayed by two or three months if the initial submission fails to list all planned manufacturing sites.

PDUFA VI further supports improvements in certain FDA operations and programs. An important initiative is to make the agency's electronic submission process more transparent and more predictable, with clear time frames for document uploads and support for advancing data standards.

New strategies aim to keep staffers from drowning in meetings. While agency officials encourage sponsors to meet early and often with reviewers to discuss and gain agreement on product development plans and protocols, these efforts have overwhelmed CDER and CBER with some 3,000 meeting requests in 2015. Agency officials seek to improve the process by resolving some issues in writing, instead of in-person meetings, and to gain more time to review the often thousands of pages of background documents prior to a meeting.

An important provision of PDUFA VI aims to improve FDA's hiring process to help bring more scientists and medical professionals into the agency. New procedures would clarify and simplify job announcements, and a new high-level agency office will oversee recruitment and retention of scientific staff. Agency expertise is critical, stakeholders agree, for FDA to meet the many goals and challenges of the PDUFA program.

FDA and industry worked hard to gain agreement on PDUFA VI fairly quickly and are looking for broad support from patients and the medical community to spur Congressional consideration of the revised program. The legislators need to reauthorize FDA fees for drugs and biologics, along with similar programs for biosimilars, medical devices and generic drugs, before they expire Sept. 30, 2017. The pressure is on because a change in administration in January will delay Congressional consideration of new programs and policies for several months.

— Jill Wechsler

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Both the EMA and FDA are in the process of rolling out new ICH technical standards for adverse event reporting and collection of data on medicines. With the ICH E2B R3 standard implementation deadline fast approaching, companies are facing an overhaul of several key ICSR processes and procedures.

During this webinar, Quintiles safety system and pharmacovigilance experts will discuss how the new standards impact day to day safety operations and outline some top tips for project managing the implementation of the new standards. We will look at systems and business processes that are impacted AND outline a plan to support compliance once the standards come into force.

Key take-aways:

- Summarize the IDMP and E2B R3 new Standards.
- Learn the impact of the new Standards on processes and procedures.
- Understand what needs to be done to prepare for implementation.

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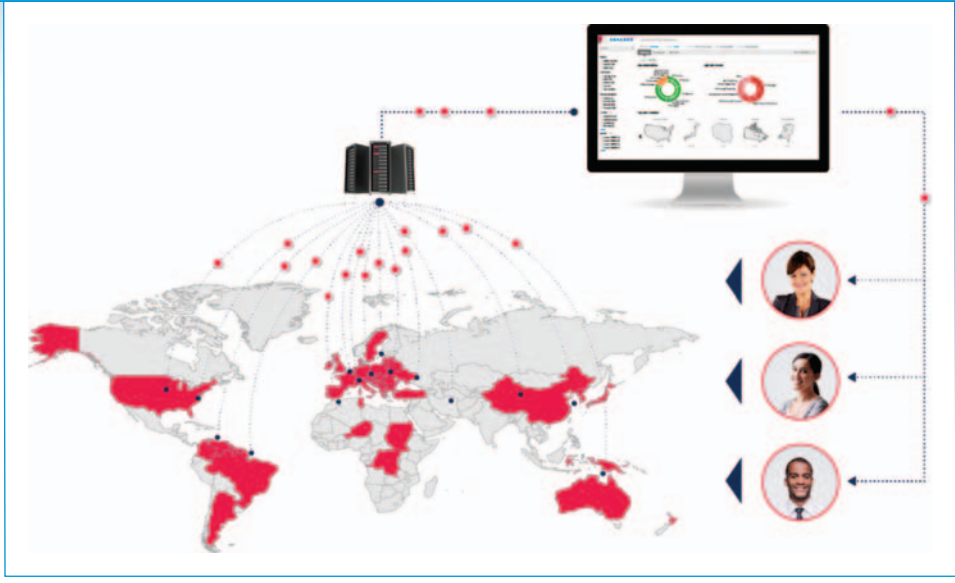
For technical questions about this webinar, please contact Kristen Moore at kristen.moore@ubm.com

An Executive Summary

Risk-Based Monitoring – Driving the Evolution of the Clinical Research Associate Role

Chris McConachy, B.Sc,
Senior Manager, Monitoring & Data Flow Optimization, Covance Inc



Over the last 10 years, clinical trials have changed substantially in response to increasing globalization and study complexity, along with new technological capabilities and industry guidelines.[1,7] With these noticeable transformations, sponsors are increasingly revisiting their monitoring methods to uncover new efficiencies and develop more robust risk management processes that can enhance ongoing patient safety and data quality.

At the forefront of this movement is risk-based monitoring (RBM) – a broad term for a variety of clinical monitoring methods that combine people, process and technology, enabling project teams and Clinical Research Associates (CRAs) to focus on the most important risks in clinical trials.

CRAs and the use of informatics technology

When RBM first emerged from industry and regulatory guidance, the need for a cost-effective, technology-based RBM solution was apparent. To address this gap, Covance developed Xcellerate® Monitoring, an award-winning analytics suite that delivers state-of-the-art data integration, supporting all aspects of central monitoring, including risk monitoring, medical review, statistical monitoring and data review.

This advanced working model is fully aligned with the FDA[2] and EMA[4] guidelines and TransCelerate principles, which encouraged pharma, biotech, CRO and ARO groups to adopt risk-based approaches in clinical trial execution – essentially directing the industry to "monitor smarter".

With an addendum to ICH GCP $(E6)_7$ planned for release in late 2016, the further adoption of RBM methods should be expected as the industry embraces advances in technology and risk management processes which offer new opportunities to enhance patient safety, increase efficiency and improve data quality.

The important role of CRAs is similarly evolving to embrace:

- **Increased Application of Specialist Skills**
  Risk-based monitoring technology platforms, like Xcellerate Monitoring, provide CRAs enhanced visibility to site performance, which permits greater focus on the patient safety and data quality aspects of clinical monitoring. Prioritizing on-site monitoring activities allows CRAs to refine and utilize specialist skills when reviewing critical data points and process compliance at the site level.

- **Greater Focus on High-Value Compliance Checks**
  TransCelerate recommends de-prioritizing Source Data Verification (SDV) for transcription errors, as they offer limited value by using approximately 10 to 15% of the trial costs for only 1.1% of the total data corrections. Instead, the practice of Source Data Review (SDR) is encouraged, an activity that involves the review of source documentation to verify

quality and ensure compliance with the protocol and critical processes.[1] By looking beyond simple transcription checks and delineating critical and non-critical monitoring targets, CRAs can conduct the vital process review activities while their project teams gain greater flexibility in customizing baseline monitoring intervention levels.

- **Adaptive and Triggered Monitoring**
  Building on the Quality by Design (QbD) features implemented during study planning phase, risk-based monitoring plans prioritize high-value monitoring activities and outline adaptive monitoring interventions for CRAs based on quantifiable site risk. Through a continual process of data-driven risk profiling that adapts as risk profiles evolve, CRA efforts can be focused on high-risk study sites—maximizing the value of CRA activities when on-site. Triggered monitoring activities through Xcellerate Monitoring also provide the CRA with an essential level of flexibility to support efficient and effective on-site monitoring during patient enrollment and study maintenance phases.

- **Shifting from an "Auditor" to a "Coach" with Increased Remote Monitoring**
  CRAs will increasingly conduct remote or "off-site" monitoring to manage administrative tasks and to conduct quantitative compliance checks that can be handled without travelling to individual sites in person. Supported by developing technologies and strengthened site relationships, remote monitoring adds valuable flexibility and efficiency to clinical monitoring methods. As a result, the CRA role is shifting from that of an "auditor" to a "coach"—actively supporting site staff to take greater ownership of process compliance and accurate data reporting.

- **Holistic Central Monitoring**
  The visibility of a trial's performance at the site and subject level is now enhanced by advanced data analytics technologies, supporting more informed decision making for clinical monitoring teams and their site-focused CRAs. At Covance, our RBM Central Monitors use Xcellerate Monitoring to identify, quantify and visualize study risks based on a continuous process of structured risk assessment. With this process, CRAs are empowered to efficiently review high-value data at individual study sites and effectively manage issues and risks remotely between on-site visits. CRAs also serve as the single point of site contact for Central Monitoring staff such as physicians, statisticians, data reviewers and RBM leads—a practice that further strengthens relationships with investigative sites.

Looking Ahead to Maximize Value and Opportunities for CRAs

The demand for robust analytics, technology and data integration capabilities continues to grow with the increasing digitalization of clinical trial data. Yet even with the expansion of remote and centralized monitoring activities, a CRA's responsibility for proper evaluation of site performance and issue management does not change. Competent and highly skilled monitors are still required to make accurate and consistent judgments.

Beyond the role of the CRA, new roles may be required within risk management teams as this holistic approach to site management evolves to include a wider range of centralized and specialized positions including specialist Central Monitors for medical, statistical or data review and RBM Data Integrators working to collectively identify and mitigate risks at all levels of the trial with a holistic approach to risk management.

Through Xcellerate Monitoring, Covance has transformed clinical trial risks into measurable returns for clinical research stakeholders with initial improvements in data quality, patient safety and cost efficiency, noting an average 20% less critical/major findings per Clinical Quality Control (CQC) visit, up to 36% lower site management spending, 18% lower travel spending and up to 66% fewer missing eCRF pages at sites—statistics that support the premise of smarter monitoring.[6]

As RBM adoption grows and becomes the industry standard for maintaining patient safety and improving data quality, CRAs face unique opportunities to thrive as clinical monitors in this shifting landscape. From leveraging analytics for data-driven decisions to adding new efficiencies with increased off-site monitoring, it will be exciting the witness the evolving role of the CRA to advance risk management and improve the conduct of clinical trials.

Learn more about the Xcellerate Informatics Suite or CRA career opportunities at Covance.com.

1. TransCelerate BioPharma Inc. Position Paper: Risk-Based Monitoring Methodology. 30May2013. Available at http://www.transceleratebiopharmainc.com/assets/risk-based-monitoring/. Accessed 02Sep2014.
2. FDA. Guidance for industry: Oversight of clinical investigations – A risk-based approach to monitoring [August 2013 Procedural]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf. Accessed 09Sep2014.
3. ICH E6(R2) Expert Working Group (EWG) Business Plan - Endorsed: 5 June 2014 Accessed: 30May2016. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Business_Plan_July_2014.pdf
4. EMA. Reflection paper on risk based quality management in clinical trials (EMA/269011/2013). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf. Accessed 30 November 2015.
5. MHRA. Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products version: 10th October 2011. Accessed 30 November 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf
6. Reference: Covance RBM White Paper: January2013. Available at http://www.covance.com/content/dam/covance/assetLibrary/whitepapers/Transforming%20Risks-Xcellerate%20Monitoring-WPCDS007.pdf.
7. Reference: ICH Harmonised Guideline: Integrated Addendum to ICH E6(R2): Guideline for Good Clinical Practice. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf
8. Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, Therapeutic Innovation and Regulatory Science 2014, Vol. 48(6) 671-680

GLOBAL REPORT

Europe's New Clinical Trials Landscape Looms Large

The clinical research community in Europe is bracing itself for major change. Clinical Trials Regulation 536/2014 is due to come into force toward the end of 2018, when the legislation becomes a regulation rather than a directive, and this development should ensure that the same rules are applied throughout the European Union (EU).

Importantly, the European Forum for GCP (EFGCP) has announced that meeting the ethical standards under the regulation will be the main theme of its annual conference, to be held in Brussels, on Feb. 21-22, 2017. The program will focus on the burning questions (and answers) for researchers, sponsors and patients.

"The regulation is now less than two years away and if we are to grasp this opportunity to improve research and regulation for patient benefit, it's imperative we look together—public, patients, researchers and regulators—at both the procedural requirements and ethical changes required," noted EFGCP in a statement.

The forum says it has taken an active role in the new regulation. Its plan at the Brussels event is to discuss procedural arrangements already underway and to address the challenges that the regulation presents, providing an opportunity for debate, as well as giving access to expertise and examples of how these challenges can be met. Workshops will be led by specialists who can offer support and solve problems.

Furthermore, the European Federation of Pharmaceutical Industries and Associations (EFPIA) has devised a list of the main characteristics of the regulation:

- A streamlined application procedure via a single entry point, the EU portal, plus a single set of documents to be prepared and submitted for the clinical trial application.
- A harmonized procedure for the assessment of applications for clinical trials, which is divided into two parts. Part I will be jointly assessed by all member states concerned, which means the countries where the trial is intended to be conducted. Part II will be assessed by each member state concerned separately.
- The involvement of ethics committees in the assessment procedure, in accordance with the national law of the member state concerned but within the overall timelines defined by the regulation.
- Extension of the tacit agreement principle to the authorization process, which will give sponsors increased legal certainty, without compromising safety, as well as streamlined safety reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states.
- Increased transparency with regards clinical trials and their outcomes.
- Union controls in member states and third-party countries to ensure that clinical trials rules are being properly supervised and enforced.

Clinical trials conducted outside the EU, but referred to in a trial application within the EU, will have to comply with the regulatory requirements that are at least equivalent to those applicable in the EU.

EFPIA sees the regulation as an opportunity to demonstrate Europe's commitment to clinical innovation, scientific collaboration and transparency of clinical trials information. To implement the regulation and achieve the core objectives, it has identified three priorities: deliver flexible, efficient and streamlined execution of the authorization procedure to avoid administrative delays; enable the required collaboration between concerned member states and sponsors; and appropriately manage the transparency of data over the life of the study.

Along with its national members, EFPIA says it is monitoring the implementation of the regulation at the national level through its National Trade Association Clinical Trials Implementation Monitor survey.

Once the regulation becomes effective, it will replace EU Directive 2001/20/EC, though clinical trials that started before the new regulation comes into force may continue to use the rules in the directive for three years from the regulation's effective date, according to the International Society for Pharmaceutical Engineering (ISPE). Sponsors can opt for the old system within one year of the regulation's effective date and operate under the directive for a three-year transition period.

ISPE points out: "The overarching change enacted by the regulation is the centralization of the clinical trial application process. Under the regulation, a proposed study's clinical trial application will be submitted electronically through a new electronic portal. The centralized submission will trigger review by representatives from the individual member states in which the sponsor is requesting the trial be conducted.

Once an application is received, a single member state is chosen to lead the assessment. The reporting member state may be the state that is requested by the sponsor, or a state may volunteer to lead the assessment. With input from other member states, the reporting state validates the application or sends queries to the sponsor requesting further details. Individual member states can refuse to authorize the clinical study in their countries.

— *Philip Ward*

Front & Center

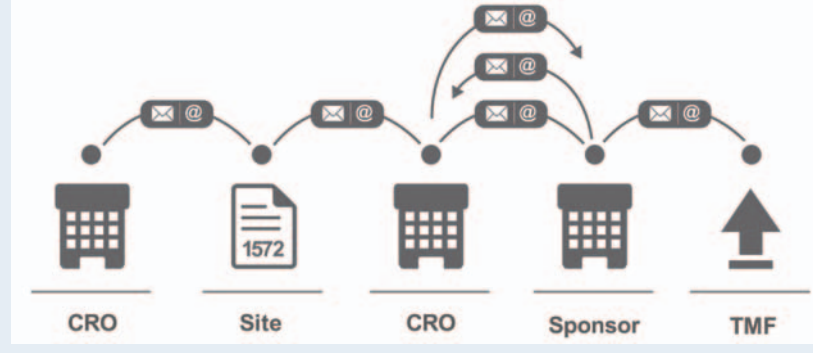
Better Together:
Start-up Content and Data
Comprehensive management and visibility of start-up activities

Site activation is a critical milestone for every clinical trial and yet most life sciences organizations rely on Microsoft Excel spreadsheets and paper processes to manage the dizzying amount of simultaneous activities required. If they are using more sophisticated systems, they likely are receiving only a window into site status.

Think what needs to happen to begin research—feasibility questionnaires have to be distributed and collected from sites; contracts have to be negotiated; clinical trial applications have to be prepared; ethics committee submissions have to be developed; investigators and clinical team members have to be trained; investigational product has to be formulated and packaged; and the list goes on.

To further complicate matters, each country has their own approval process to activate a site. Given the global nature of clinical studies, it's not uncommon for more than a dozen countries and 50 sites to be involved in a study. When a contract research organization (CRO) is involved—as is so often the case today—even more team members are added to the mix. It's no wonder Excel is not up to the task.

One of the biggest flaws with the conventional approach to study start-up is that it doesn't provide a detailed picture of start-up documents and operational data at the same time. Team members simply don't have the information they need to properly prioritize their work, and the systems employed often do not help manage the work processes involved. Automating simple workflows, such as routing documents for approval or quality control, can have a large impact on time to first patient/first visit.



A typical industry process to receive one essential document from one site. To get a true scope of the problem, imagine using a spreadsheet to track this process across 50 sites with additional emails to clarify questions about incomplete or missing documents.

Another area that bogs down site activation is staying up to date with changing ethics committee and competent authority requirements across the globe. Each country has their own rules to protect patients, and pulling together and submitting the paperwork to receive permission to conduct research in each country can be incredibly time consuming. Especially if documents need to resubmitted because the rules have changed.

Given this current state, the Veeva Vault team saw an opportunity to leverage their experience to help sponsors and CROs find a more efficient study start-up solution. Vault Study Startup accelerates the time to site activation by bringing documents and data together to provide a single source of truth and allow all team members, from all geographies, to see what they need in one place and take action on it. Sponsors, CROs, and local study team members can update documents and operational data at that central source and manage workflows and work processes, including ethics committee approvals in over 30 countries.

This single source of truth improves visibility and control, and helps maximize the recruitment window to accelerate the time to site activation. Visit veeva.com to learn more about how Vault Study Startup can help you accelerate your time to site activation.

CRO/SPONSOR

Lean Outsourcing Models for Clinical Trials

A number of recent trends within the industry, including reduced headcounts and an increased focus on "nimble" product development strategies, have prompted many companies to pursue "lean" models for the outsourcing of clinical development. Potential advantages of such models include resource and geographic adaptability, reduced fixed resource consumption, and use of "best-in-class" resources for each task, whereas perceived challenges include a lack of "tight control" over outsourcing partners, a tendency for sponsor staff to revert to traditional behaviors despite resource reductions, and difficulty finding personnel experienced in such models.

On behalf of Purdue Pharma, The Avoca Group gathered experiences from companies that have evaluated and employed lean models. Interviews were conducted with management representatives from 14 sponsors and three CROs that are currently conducting clinical development using "lean" models. For the purpose of this project, "lean outsourcing models" included any designed by sponsors to reduce or minimize the level of resources used for CRO oversight compared to traditional, "standard" models. Respondents were asked to describe their models in detail, including the responsibilities held and value added by each party; the decision criteria that led to choice of the models; and their histories with the models, including facets that have worked well, and challenges. Specific tools, technologies, and best practices used for oversight, and specific traits of sponsor personnel that work most effectively under the models were also discussed.

Rationale for lean models

For some of the smaller sponsors interviewed, development of a full-capability internal clinical research staff was never part of their corporate strategy and would not have been practical; thus they had always employed "lean" outsourcing models. Other companies had originally performed clinical trials using in-house staff and/or more "traditional" outsourcing models, but had moved at least some portion of their trials to leaner models because of headcount reductions and/or other budget constraints, a strategic mandate to refocus internal staff into areas of higher value add, movement toward increased (or increasingly variable) volumes of clinical development activity, and/or dissatisfaction with the quality or efficiency obtained using traditional outsourcing models. Positive results were reported to include not only greater efficiency in use of both sponsor and CRO resources, but also improved/faster problem-solving with fewer escalations; improved chemistry across sponsor-CRO teams; and improved ability to utilize lessons learned due to increased commitment to the relationship.

Success factors for lean models

Through the interviews, it became clear that successful lean outsourcers had made carefully considered decisions in each of seven key areas, as follows.

#1: Core competencies to retain in-house

Sponsor executives reported that their companies had made carefully-considered decisions about the functional competencies that would be retained in-house. For regulatory reasons, all maintained at least project management/oversight in-house; the nature of any other competencies retained in-house was driven by corporate strategy regarding areas of internal expertise thought to provide competitive advantage and/or by historic factors, i.e., past difficulty outsourcing successfully in certain operational areas, and/or strong desire to retain current functions for which highly skilled and experienced staff were already in place.

#2: Functional vs. full-service

Some sponsor companies were satisfied with their CROs and found the full-service model to be simple (seamless, coordinated) and relatively resource efficient (internally), whereas others preferred to outsource functionally to what they believe to be best in class. Companies reported success with both strategies; considerations included the volume of work that could be committed to a provider (i.e., desire not to dilute volume if it's already low), and process-related considerations (i.e., if highly specialized expertise, training, requirements, and/or processes are needed across programs, it can be easiest to outsource functions to the same provider across programs).

#3: Number and types/sizes of CROs to engage

Sponsors took a variety of approaches to determine the numbers and types/sizes of CROs to work with under their lean models. Some, particularly those with narrow therapeutic foci and those transitioning from intensive oversight models, chose to work with only one. The rationale being that that lean outsourcing models require a level of trust and understanding of sponsor expectations that are difficult to achieve with more than one CRO at a time, and that lessons learned from a pilot could be applied to others in the future.

#4: Use of independent contractors and/or specialty shops

The effective use of independent contractors was a nearly ubiquitous theme among successful lean outsourcers. As a means

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Presenter:

Suneela Thatte
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Moderator:

Lisa Henderson
Editorial Director, Applied Clinical Trials

After a couple of challenging years for the clinical research fraternity in India brought on by uncertainty and unpredictability in the regulatory environment, the Indian regulators have recently introduced several positive changes and modifications in existing rules and regulations. The changes have made way for a more robust patient-centric regulatory framework that is guided by science and rational thinking. This webinar will discuss the recent clinical research regulatory changes in India and what this means for those doing or interested in doing clinical research in the country.

The webinar will address 2 key areas:

Overview of regulatory changes in India

- Before 2015, challenges existed in India around uncertainty in the clinical research regulatory environment, particularly around compensation, audio visual recording of informed consent and the review process.
- As a result of collaboration and engagement by the India regulators with stakeholders, many of these challenges have now been addressed and additional guidelines introduced to ensure a more robust and transparent regulatory environment. This session will address all the changes in the last two years.

The impact and implication of these changes

- This session will address the implications of the changes discussed in the earlier section, what these changes translate into from a practical standpoint and what this means for those conducting or contemplating conducting clinical trials in India.

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of augmenting sponsor capabilities when necessary, independent contractors tend to be stable and reliable resources, have a relatively high average experience level per dollar, and be role-flexible. These traits can help to offset turnover, and the use of mixed teams can be effective means of raising the bar for all staff.

#5: Types of trials to outsource under the lean model

Although some sponsors outsourced exclusively using lean models, others used lean models only for a subset of their clinical trials. Decisions about which trials to outsource using lean models were generally made based on considerations surrounding phase, therapeutic area and region, as well as internal resource availability. Some companies used a cost-based approach, finding it more cost-effective to manage different types of trials under different models. Others used a risk-based approach, for example using lean models for regionally limited vs. global trials; less complex protocols, indications, or populations; and lower priority portfolio assets or phases.

#6: Contractual provisions

Sponsors generally reported positive experiences with carefully conceived risk-sharing models, and those that had not incorporated such contractual provisions generally expressed regret. Risk-sharing contractual provisions can work best with lean oversight models since these reduce the probability that CRO performance will depend upon sponsor involvement at a large number of touch points. Options reported to work well included both fixed-price models and risk-sharing models, whereby CROs had access to bonuses in exchange for meeting performance targets and/or suffered penalties for not doing so.

#7: Supporting tools and best practices

The effective use of tools and best practices was found by most of the participants in this research to be critical when operating under a lean model. Such tools/practices included: a playbook or manual that describes, in detail, the roles of CRO and sponsor team members); standards and/or expectations for specific functional tasks, deliverables, and staff qualifications; communication and escalation plans; and risk assessment and management activities.

— *Denise Calaprice, PhD, is Senior Consultant, The Avoca Group; Mitchell Katz, PhD, is Head of Clinical Research & Drug Safety Operations, Purdue Pharma*

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DATA ANALYSIS

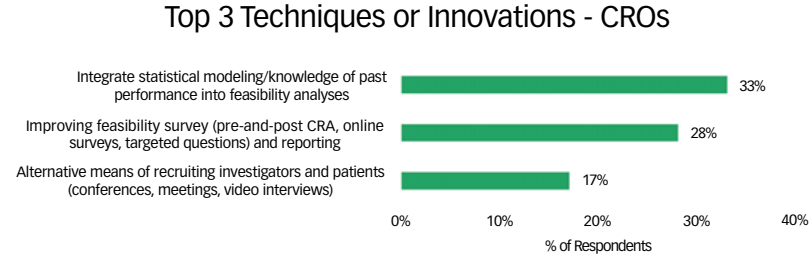
Best Practices in Study Feasibility

Successfully navigating the medical, clinical, logistical and regulatory challenges associated with establishing the feasibility of a clinical trial is not easy. Insights from sponsos, contract research organizations (CROs) and sites have been compiled in ISR's *Best Practices in Study Feasibility* report. A particular area of interest for readers of the report are the techniques and innovations proffered by sponsors and CROs for conducting feasibility analyses. Both groups identified that the integration of statistical modeling and knowledge of past performance into feasibility analyses is positively impacting the process.

Sponsors also see value in making direct, personal contact with investigators to build better relationships and a greater use of electronic medical record (EMR) data as positive innovations. CROs point to improved feasibility surveys and better targeting questions as ways to improve study feasibility estimations. ISR also collected insights to improve the accuracy of study feasibility estimates including: the percentage of trials that require a feasibility analysis, and whether the analysis is conducted in-house or outsourced; awareness of feasibility analysis service providers and frequency of use; and the data sources utilized for feasibility analyses and a ranking of which data sources contribute to the accuracy of the estimate.

— ISR

Most-liked Methods for Feasibility Analysis



Source: Industry Standard Research; www.isrreports.com/reports/best-practices-in-study-feasibility

Survey response breakdown (sponsor n = 60, CROs n = 18)

REGULATORY

FDA Includes First PRO Measure for COPD

Chronic obstructive pulmonary disorder (COPD) is on track to be the third leading cause of death worldwide by 2020. Beyond the currently approved drugs, which treat the symptoms of the disease, there are limited drugs that address the underlying inflammation of COPD or affect disease progression. In May, the FDA issued its first update to the draft guidance on developing drugs for COPD since 2007.

Of note, the guidance includes the use of a patient-reported health-related quality of life questionnaire—The St. George's Respiratory Questionnaire (SGRQ). According to an FDA press release, the SGRQ has been used extensively since its introduction 20 years ago, and has large support among COPD experts as a key endpoint toward developing new COPD drugs.

Kai-Michael Beeh, MD, founder and medical director of the Respiratory Research Institute in Wiesbaden, Germany, told *Applied Clinical Trials* the new FDA guidance reflects the knowledge gained in the past nine years since the original draft guidance was released. Beeh says the update allows for other endpoints in COPD trials that are not just granted on lung function. "It's a step forward and offers encouragement to use stratification in clinical trials and increase the likelihood of success."

However, diagnosing COPD in patients remains an obstacle. As pointed out in *The Lancet Respiratory Medicine* Commission's recent 54-page report, "Meeting the challenge of COPD care delivery in the USA: a multiprovider perspective," patients report delays in diagnosis of, on average, two years and nine months. Patients cited delay factors including their own belief that early symptoms were due to decreased fitness, being overweight, or ageing, especially those who were current or former smokers.

Another problem, according to the report, is the spirometer, which measures forced expiratory volume (FEV) to determine lung function. Primary care providers note they lack trained staff, training for results interpretation, and in-office time to conduct spirometry tests, which can lead to both under- or over-diagnosis of COPD. Achim Schulke, EVP of Respiratory at ERT Research, told *Applied Clinical Trials* that spirometer use in clinical trials would suffer the same fate if left to untrained staff and interpretation.

— *Lisa Henderson*

SUBJECT ENGAGEMENT

The Growth of Direct-to-Patient Trials

Recently, the direct-to-patient (DTP) model, which brings certain medical procedures and protocols to a patient's home, has emerged as a popular solution. In 2015, the Medical Research Network (MRN), a provider of home healthcare for patients in clinical trials, entered a partnership with World Courier, a global specialty logistics company and a part of AmerisourceBergen, to elevate the reach and effectiveness of DTP clinical trials. The partnership's aim is to increase patient recruitment and retention and provide an integrated supply chain in the transportation of patient samples and the storage and distribution of investigational medicinal products (IMPs).

In the following Q&A, Michael Sweeney, senior director of global service development at World Courier, and Stuart Redding, vice president of global business development and marketing at MRN, share insights on the evolution of community-based trials.

Q: *How does the* DTP *model improve the recruitment and retention of qualified patients*?

REDDING: As clinical trials continue to grow more complex, patient recruitment and retention will remain a major challenge that sponsors face. Today's protocols are more demanding than ever and frequent travel to a clinical site can deter patients from long-term participation in studies, especially when the site is far from their homes. In fact, about 25% of patients drop out before study completion.

In many studies, as many as 50% of the visits could be relocated to a patient's home. The added convenience is a critical factor in retaining patients, who otherwise might have to regularly travel to a clinical trial site for procedures, such as IMP administration, that can take hours to complete.

Q: *How do organizatons ensure the clinical products are safely transported in a timely manner*?

SWEENEY: When more home visits are incorporated into trials, nurses or courier drivers may travel long distances to a patient's home. Some trips require flights, while others call for long drives to remote areas. In order to reduce the number of deliveries, we are in the process of deploying small, temperature- and access-controlled refrigerators in patients' homes. The solution stores medication securely and at an optimal temperature, providing in-home access to the product. It features a real-time remote temperature monitoring system as well as security features and inventory management capabilities that to track product access. We've found that such in-home solutions help improve patient adherence and reduce medication waste.

REDDING: Every home visit requires a coordinated approach from all stakeholders—which includes nurses, the pharmacy, the logistics company, the site and the central lab—to ensure IMP is delivered from the pharmacy to the patient's home on time, at the appropriate temperature and in the perfect condition, no matter the distance.

When planning the home visits, the entities must understand the temperature control and monitoring needs of the product being delivered, identify an appropriate packaging solution and outline the specific timing. Given all the potential variables, flexibility is critical to our success. That's why we develop detailed contingency plans for all studies to ensure we are prepared to overcome any unforeseen obstacles.

Q: *Varying country regulations, compliance with* GxP *policies and global logistics support are often the main challenges associated with the* DTP *model. How can sponsors overcome those hurdles*?

Michael Sweeney

Stuart Redding

REDDING: Perhaps the most important step is partnering with a home trial company early in the process, in order to maximize the number of home visits and gain insight into the regulatory landscape. Such companies that bring an in-depth knowledge of the countries they operate in can help ensure adherence to both good clinical practice standards and local market regulations. It's critical for sites to be well-educated in the homecare service as well. For example, they need to understand who is seeing their patients, how their source data will be provided and what their responsibility is to maintain oversight of the patient's progress.

SWEENEY: Partnering with a specialty logistics company that has an understanding of the requirements and a local presence in the market can be extremely helpful for sponsors, especially smaller biotechnology firms that may have limited resources or exposure to a country's regulatory environment. Regulatory requirements and import procedures related to clinical trial products vary from country to country and are subject to change. Through integrated, GxP-compliant supply chain solutions, specialty logistics partners can meet the quality requirements and ensure the integrity of products and chain of custody.

— *Michael Sweeney and Stuart Redding*

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Dr. Paul Strumph
Vice President, Clinical Development, Lexicon Pharmaceuticals

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Finally, Standardized KPIs are Front and Center

Most firms are now using a standard set of key performance indicators

During the past 15 years, my teams at the Tufts Center for the Study of Drug Development (Tufts CSDD) have frequently encountered organizations struggling with the collection and application of meaningful and relevant management metrics. These struggles have largely been specific to each given company's culture and operating structure: In the past, it was not unusual to find companies participating in Tufts CSDD working group studies who are not actively collecting certain management-level metrics. On the opposite end of the spectrum, some participating companies have appeared to be collecting too much performance and quality data, often without a clear sense for its purpose. In many cases select financial and quality metrics have been too difficult for many organizations to collect, as this data resides in separate functions and cannot be accessed easily.

Perhaps one of the largest challenges for organizations has been benchmarking multi-company performance, efficiency and quality metrics. Ten years ago, Tufts CSDD working group companies each defined their operating level metrics differently. Wide variation in metrics-gathering practices was observed not only at the corporate level but also between functional areas and even clinical teams. These conditions made it very difficult to compare project performance and quality within a single company and across peer companies. As a result, Tufts CSDD frequently had to assist participating companies in establishing and collecting consensus-defined metrics. Over time, my study teams routinely turned to standardized performance and quality metrics developed by the Metrics Champion Consortium (MCC) to support our research activity.

Although the drug development enterprise has been slow to adopt standardized performance and quality metrics definitions, progress has been made. Indeed, a new study just published by the MCC suggests that the majority of companies are now using a standard set of senior-management level key performance indicators (KPIs) and adoption of functional level standardized performance metrics has reached an inflection point.

Adoption drivers

A confluence of factors has no doubt contributed to widespread adoption of standardized metrics. To name but a few: the growing use and coordination of eClinical technology solutions has made data capture and access easier and more convenient. Facing perennial operating challenges—including clinical project delays; high staff turnover and workload; longer cycle times; poor patient recruitment and retention rates; high levels of unanticipated protocol amendments and change orders; and the rising cost of clinical trial management and support—sponsors and contract research organizations (CROs) are hypersensitized to monitoring performance and quality actively.

Kenneth A. Getz
MBA, is the Director of Sponsored Research at the Tufts CSDD and Chairman of CISCRP, both in Boston, MA, e-mail: kenneth.getz@tufts.edu

Increasing awareness of the root cause drivers of poor development performance and economics has also stimulated management interest in gathering metrics and analyzing organizational practices, behaviors and activities. A growing body of research conducted during the past 15 years shows that protocol complexity is highly associated with clinical trial performance, quality and cost. Protocol designs that include a relatively large number of eligibility requirements and unique procedures conducted frequently have more delays, lower study volunteer recruitment and retention rates, higher average numbers of protocol amendments and protocol deviations, and generate lower quality clinical data than designs without such features.

As an aside, a 2016 Tufts CSDD soon to be published indicates that protocol complexity—as measured by the number of unique procedures, total procedures performed, eligibility criteria, planned study volunteer visits—is not only rising, it is accelerating, largely in response to demand for data to support more secondary, tertiary and exploratory (i.e., "non-core") protocol endpoints.

Rising reliance on outsourcing and the use of more collaborative partners to support drug development activity has also contributed to growing demand for management metrics at both the senior level and day-to-day operating level. Performance data transparency has become essential to expectation setting, routine relationship management and incentive tracking.

Regulatory agencies and public-private partnerships have also contributed to the adoption of standardized metrics. Agencies have released guidance and regulations encouraging the clinical research enterprise to build practices ensuring a higher level of quality

into development planning to drive downstream efficiency and performance. The Quality by Design (QbD) movement, formally introduced in 2011, incorporates quality and risk-management principles into clinical trial oversight and execution. During the past several years, both TransCelerate and the MCC have launched risk assessment and risk mitigation tools to assist pharmaceutical and biotechnology companies in assessing and managing project- and protocol-level risk and quality (e.g., lower error rates, higher compliance and better patient safety) prior to initiating clinical trials.

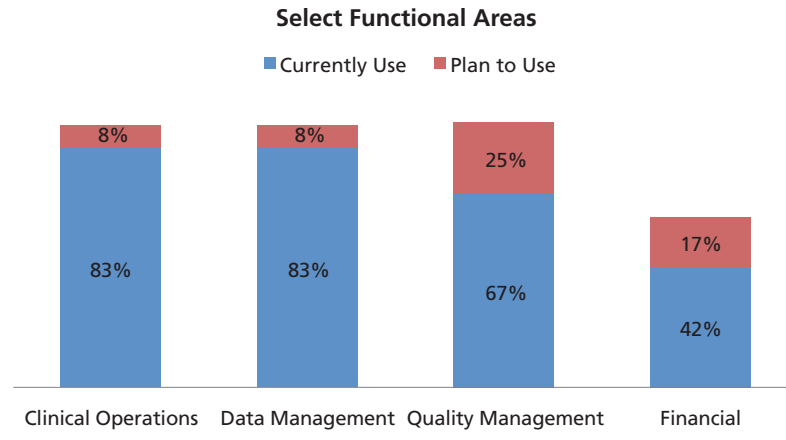
The 10th anniversary of the MCC's founding is yet another indicator of the growing recognition by clinical research professionals of the importance of standardized operating function-level and corporate-level performance metrics. More than a hundred companies are participating MCC members. And several years ago I joined the MCC board to reflect my personal commitment and belief in the critical need for, and benefit of, standardized benchmark performance measures.

Majority using KPIs

The results of a new 2016 MCC survey conducted among 44 predominantly large and mid-sized companies (with 2,500 total employees or more) are striking. At this time, nearly two-thirds of organizations surveyed report that they are now using a standard set of senior management-level KPIs. The majority of organizations (73%) review these metrics at least on a quarterly basis. In addition, about half of sponsor companies report setting annual operating performance goals and developing improvement action plans using end-of-year KPI results.

Companies responding to the survey indicated that they are using an average of eight senior-level KPI metrics that measure a variety of areas, including clinical operations, data management and quality assurance/quality control. The most common metrics include:

Current Adoption of Standardized Performance Metrics



Source: MCC, 2016 survey among 44 pharmaceutical and biotechnology companies

- Proportion of final databases locked on time
- Mean number of protocol amendments post-protocol approval
- Proportion of studies completing patient enrollment on time
- Mean number of protocol deviations per study volunteer
- Proportion of studies with investigative sites activated on time
- Mean number of times databases are unlocked per study
- Proportion of vendors with critical findings following an audit

At the functional level, the use of standardized performance metrics is very high in clinical operations and data management departments. More than 90% report currently using (83%) or planning to use (8%) standardized metrics. The most common clinical operations metrics—some that flow into corporate level oversight—include the percentage of studies completing enrollment on time; the percentage of studies activated on time and the percentage of regulatory packets approved the first time. For data management, the percentage of final databases locked on time and the percentage of case report forms finalized on time are among the most commonly used standardized metrics.

The MCC is releasing a full report on the results of the 2016 survey on its website followed by articles published in trade journals.

Up next

The International Conference on Harmonization (ICH) is expected to release its R2 guideline in November. This new guideline replaces the one implemented in 1997; accommodates the scale and complexity of current drug development strategy, management and practice; and promotes better data quality and human subject protection through the integration of risk-management processes.

With cloud-based technologies and the availability of ever-larger databases of structured and unstructured data and information, the opportunities are even greater for rich and robust performance analytics to inform the management and execution of increasingly open collaborative teams. Newer technology solutions will enable sponsors and their partners to identify leading standardized risk and ultimately standardized predictive indicators.

These are exciting times for the drug development enterprise. Selfishly, this is particularly welcome news for those of us actively involved in benchmarking enterprise performance and practice

Assessing Global Clinical Supply Logistics

Mary Jo Lamberti, Richard Hsia, Cheryl Mahon, Christine Milligan, Ken Getz

Study collects first comprehensive metrics on current supply management and distribution practices.

Global clinical supply professionals are driven by a simple credo: to provide the highest possible quality clinical trial supplies in a fast and efficient manner. Given the scope of global clinical trial activity today, delivering on this credo is a tall order. There are approximately 40,000 unique investigators worldwide conducting at least one FDA-regulated clinical trial.[1]

There are a number of factors intensifying pressure on global clinical supply professionals. To mention a few key factors: the economics of supply chain management and distribution have grown substantially due to study complexity and increases in shipping costs, labor costs, technology solutions costs and changes in drug therapy properties requiring additional shipping and packaging considerations (e.g., cold chain and temperature sensitive shipping requirements; combination therapies; and companion diagnostics).[2] A recent survey of 250 supply chain executives found that two-thirds anticipated significantly increasing spending on clinical trial logistics over the next two years.[3]

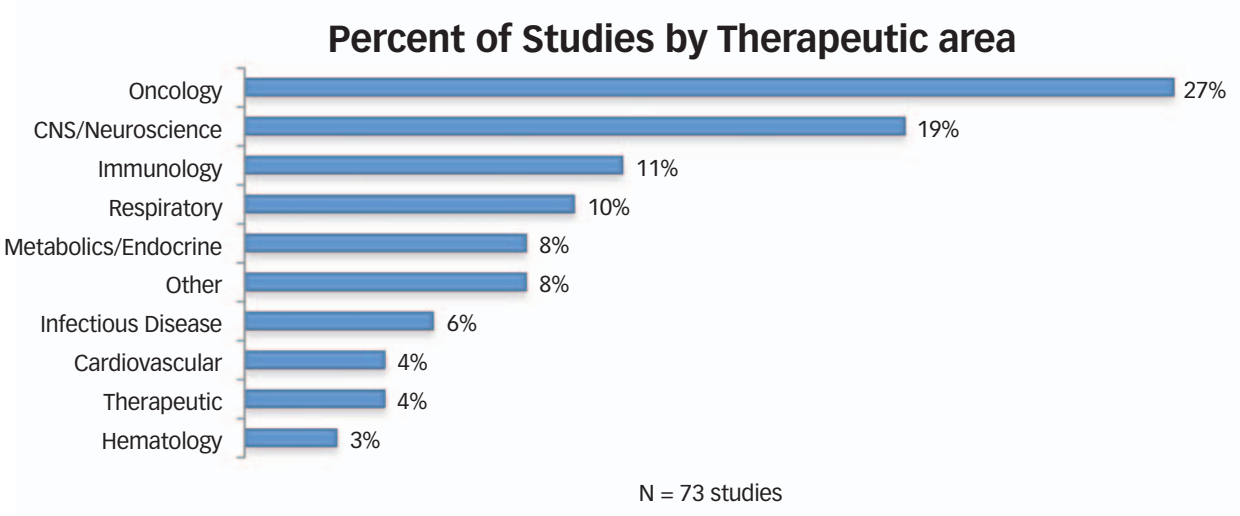
Investigative site workload has increased substantially, making it more difficult to receive operating support from study staff. A Tufts Center for the Study of Drug Development (Tufts CSDD) study examining protocol complexity and burden on clinical trial site staff, for example, found that investigative site work effort to administer each protocol had increased 64% between 2002 and 2012.[4,5] Short study start-up lead times, more complex study drug packaging requirements and tight study conduct durations place significant pressure on supply chain managers to provide efficient supply ordering and tracking solutions for investigative sites to use.[6]

Increasing demands from global regulations are also impacting the supply chain. In 2013, the European Union enacted good distribution practices (GDPs) which are becoming the adopted guidance globally.[7,8] Although the timeline is still under discussion, new regulations for clinical trials conducted in the European Union will occur in October 2018.[9] This new law could potentially impact the supply chain, although it is primarily geared to existing good manufacturing practices (GMPs) for products covered by an existing directive.

Clinical supply professionals face ongoing risks to the supply chain security, traceability and authentication of a product. There are constant threats of counterfeiting, which can impact patient safety.[10] At the same time, clinical supply logistics managers face substantially higher levels of visibility and demand to play a more strategic role within their organizations.

Despite the heavy and increasing pressure on clinical supply chain professionals, there is little to no historical data characterizing performance, measuring the impact of new processes and solutions and identifying areas of improvement. In response, Tufts CSDD—in collaboration with a diverse group of pharmaceutical and biotech

Study Therapeutic Areas



Source: Tufts CSDD

Figure 1. The breakdown of therapeutic areas studied by the logistics survey respondents.

companies, clinical supply logistics providers and suppliers—conducted a global clinical supply logistics study. The study gathered survey data and clinical study performance data from companies in order to examine current management practices and strategies that have been implemented to enhance efficiency and productivity within the clinical supply logistics area. The results of the study suggest that companies are implementing a variety of strategies that, together, are assisting organizations in maintaining high quality and low error rates and identifying contributing factors for waste. All sponsor companies, however, are encountering wide variation in mean shipping times.

Study methods

Tufts CSDD convened a roundtable meeting with global clinical supply managers and directors to identify the most critical areas for which benchmark data could be gathered. Later, the group narrowed the list of topics to the focus of the current study. A total of 15 companies participated in the study, including Astellas, AstraZeneca, Biogen, Bristol-Myers Squibb, Eli Lilly, Janssen (a Johnson & Johnson company), Merck Serono, Pfizer, Sunovion, UCB, Catalent Pharma Solutions, Fisher Clinical Services, Clinigen Group, Medidata Solutions, and Endpoint Clinical. This working group collectively developed both a survey and a data collection instrument. The study aims were to gather quantitative metrics and to capture practices and strategies regarding clinical supply logistics. The study focused on warehousing and distribution and did not examine supply sourcing, manufacturing or packaging and labelling.

The study examined a number of areas within global supply logistics, including management of distribution strategies among organizations and measures of success of these strategies. Approaches to temperature monitoring and implementation of cost-reduction measures were also investigated. Lastly, use of interactive response technologies (IRT) and other tools used to increase inventory visibility and study supply forecasting were explored as part of the study.

> **Clinical supply logistics managers face substantially higher levels of visibility and demand to play a more strategic role within their organizations.**

Tufts CSDD facilitated the working group process and collaborated on the development of the survey and data collection instrument. All data was gathered and analyzed by Tufts CSDD. The study was launched in the fall of 2014 and data was gathered through early 2015. A preliminary results meeting was held in London in June 2015 and a final results meeting was held in Boston in October 2015 with working group companies to discuss the results of the analyses.

The survey gathered demographic data on respondent's organization type and size, the top therapeutic areas in which clinical trials are being conducted at their organization, and countries to which their organization is send-

Enrollment Time Variance

TA	N	Maximum	Minimum	Range	Mean	Standard Deviation	Mode	CoV
Cardiovascular	2	14	12	2	13.0	1.4	12	0.1
CNS/Neuroscience	14	40	4	36	15.9	12.7	6	0.8
Hematology	2	4	4	0	4.0	0	4	0
Immunology	8	24	2	22	12.4	7.2	10	0.6
Infectious Disease	3	21	17	4	19.7	2.3	21	0.1
Metabolic/Endocrine	6	18	1	17	9.7	7.2	1	0.7
Oncology	13	36	3	33	14.9	11.5	3	0.8
Reproductive	2	3	3	0	3.0	0	3	0
Rheumatology	1	3	3	0	3.0	0	3	0
Respiratory	6	24	6	18	13.8	5.8	14	0.4
Other (unspecified)	3	17	2	15	8.7	7.6	2	0.9

N=60 studies

Source: Tufts CSDD

Figure 2. Variance in enrollment time (months) by therapeutic area.

ing drugs and supplies. Data was also gathered on depot locations and regional hubs; distribution networks and strategies; return management; temperature sensitive shipping, use of IRT; inventory and planning systems; and training and communication. The survey was sent via an email invitation to select company contacts as well as to the working group companies. In addition to the working group, there were 97 invitations sent out across the industry, to pharmaceutical companies, contract research organizations (CROs) and service providers, asking potential respondents to complete the survey. A total of 17 respondents completed the survey.

In addition to the survey component, data on clinical supply logistics were gathered for recent clinical studies conducted by the working group companies. These data examined global studies conducted by companies in the past five years. Organizations were asked to contribute data from at least eight of their studies (two trials per phase) across a broad range of therapeutic areas.

The data collection instrument gathered clinical study-specific cycle time and performance data from participating companies. Data was gathered on study characteristics, including study phase and status, therapeutic area, disease states, global sites and planned enrollment. Data on key metrics included number of shipments, on-time shipments, cycle times, product impact, waste, costs spent on study services and outsourced logistics services. After an interim results meeting, working group participants agreed to provide additional data on product impact, waste and shipping times based on refined definitions. Additional data was contributed by 12 working group companies. These data are included in the current analyses in this article.

> **Despite the heavy and increasing pressure on clinical supply chain professionals, there is little-to-no historical data characterizing performance.**

Results and study data analyses

Seventeen companies responded to the logistics survey and 12 companies provided logistics data for 73 clinical studies across a diverse group of therapeutic areas, including oncology, neuroscience and central nervous system (CNS), immunology and respiratory studies. Of the 73 studies gathered, there were 14 (19%) in Phase I, 19 (26%) in Phase II, 31 (42%) in Phase III and nine (12%) in Phase IV. (Some companies contributed less than two studies per phase as additional data were not available). The top therapeutic areas of studies gathered were oncology, CNS and neuroscience, immunology and respiratory (see Figure 1 on page 27). For all study data gathered, companies sent drugs and supplies to 5,682 sites across all global regions. Shipments were distributed across North America, Western and Eastern Europe, Asia-Pacific, Latin American and "Rest of World."

The mean planned enrollment time of studies in Phase II and Phase III were 11.8 months and 16.3 months, respectively. Variance in enrollment time across studies from 11 therapeutic areas was small, ranging from 0.1 to 0.9 (see Figure 2). The variance in enrollment drives clinical supply logistics strategy and performance. The studies in CNS and neuroscience, oncology and metabolic and endocrine areas had high variances, while hematology and infectious disease had low variances.

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For technical questions about this webinar, please contact Kristen Moore at kristen.moore@ubm.com

Usage of IRT Systems

IRT System Usage by process	N:Total
Drug Ordering	12:12
Randomization	10:12
Data Extension Management	8:12
Drug Reconciliation	7:12
Temperature Excursion Tracking	5:12
Other	4:12

Other Processes

- Blind Break and Drug Assignment
- Disposition of Temperature Excursion
- Local Depot Re-supplies (depot to depot transfers)
- QP/GMP Releases
- Randomizing and tracking visit Schedules
- Subject Dosing
- Subject Status
- Data Transfer to demand planning system

	Mean	Standard Deviation	CoV	Minimum	Maximum	Mediam	Range
Percent of Studies Using IRT Systems	67.5%	18.9	.3	30%	90%	75%	60

N=12 companies

Source: Tufts CSDD

Figure 3. Respondents estimated that nearly 70% of studies were using interactive response technologies (IRT) for multiple processes.

Distribution strategies

Survey respondents indicated that drugs and supplies were shipped across all regions with the largest proportion of shipments in North America (78%), followed by Western Europe (66%), Eastern Europe (63%), Latin America (29%), Asia-Pacific (22%) and Rest of World (18%). (Percentages represent percent of total shipments and do not add up to 100%). Companies reported that their top regional hubs are in Western Europe (38%), Asia-Pacific (31%) and the Rest of the World (13%). Top local depot locations are in Latin America (49%), North America (41%) and Asia-Pacific (36%) regions. Distribution strategies varied with 31 studies (42%) using a centralized approach, 30 (41%) were managed regionally and 12 (16%) were locally managed. A centralized approach is defined as one depot for a global study distributing to all sites. Regional hubs were defined as the main distribution hub responsible for shipping to each country within a wider region, and local depots were depots with regular shipping only to domestic locations.

IRT systems

Respondents estimated that nearly 70% of studies were using IRT systems for multiple processes, including drug ordering, randomization and expiry data management. Data was gathered from 12 companies for this question. Other usage of IRT systems were in the areas of drug reconciliation and temperature excursion tracking (see Figure 3). The majority used IRT for drug ordering (12 of 12 companies), randomization (10 of 12) and data extension management (eight of 12). IRT is also being used for effective control of blinding and unblinding, as it hosts dosing assignment information, instead of paper-based control. The primary ways that companies envision the use of IRT evolving in their organization were through new functionalities and standardized modular platforms. Staff from clinical supply and clinical operations were identified as primary decision-makers in outsourcing or keeping IRT systems in-house.

> IRT is also being used for effective control of blinding and unblinding, as it hosts dosing assignment information, instead of paper-based control.

The results of the survey also suggest that use of IRT and integration are two approaches that have increased inventory visibility within organizations. Being able to integrate multiple systems (for example, an integrated EDC/IRT approach) provides access to all sources of data. Survey respondents indicated that they used multiple systems, ranging from one to six, and the majority of these systems are outsourced. Some of the platforms were integrated with IRT and included EDC, drug accountability and enterprise resource planning (ERP).

Investigative Site Shipping Logistics

Mean Shipping Time in Days by Distribution Strategy

		North America	Latin America	Western Europe	Eastern Europe	Asia/Pacific	Rest of the World
Centralized N=27 Studies	Mean	5.8	16.2	2.8	2.9	19.8	27.8
	Median	1.7	3.6	2	2	5.5	43
Local N=11 Studies	Mean	1	2	2	1.5	1.5	2.5
	Median	1	2	2	1.5	1.5	2.5
Regional N=19 Studies	Mean	1.2	1.7	1.7	1.5	1.8	1.8
	Median	1	1.5	1.5	1.5	1.5	1.5

Centralized Strategy Analysis

Mean	Standard Deviation	CoV	Minimum	Maximum
12.5	10.3	0.8	2.8	27.8

Source: Tufts CSDD

Figure 4. The wide variation in mean shipping time is presented.

Many companies report IRT improvement initiatives in new systems or processes through standardization of requirements, interfacing with other clinical systems or revising system specification processes or functionalities. Also, cross-functional governance teams are in place at most organizations as part of improvement initiatives that oversee functionality standards and processes internally as well as with vendors. Lastly, IRT improvement initiatives for provider and partner evaluations were also being implemented. Examples of these initiatives included providing formal training and improving IRT standards among sponsors, CROs and IRT providers.

Site shipping logistics

For the 73 studies evaluated, there were 1,538 shipments, on average, made to investigative sites and 17 bulk shipments to in-country depots in our analyses. An overwhelming majority of shipments—97%—arrived on time to sites and 80% to in-country depots. We also found that in analyzing mean shipping time in days by distribution strategy that there was a wide variation and the longest times were found in centralized approaches (5.8 days in North America to 27.8 days in Rest of World) or one depot for a global study distributing to all sites (see Figure 4). Distribution strategies were divided among centralized (27 studies), local (11), and regional (19) approaches.

Costs, shipments and product impact

The largest proportion of clinical supply logistics costs across all clinical studies analyzed were for courier and depot costs (49%) and storage and distribution costs (40%).

> An overwhelming majority of shipments—97%—arrived on time to sites and 80% to in-country depots.

Of the total studies, 43 were outsourced and 30 were run internally. A small percentage of total studies (3%) from the company data gathered experienced product impact with the greater number of reports involving errors in shipping and handling, including temperature excursion. Other errors included site mishandling, customs intervention and errors with IRT. Errors with packaging in labelling are among the least (see Figure 5 on page 32).

Waste and overage

Product waste was examined across studies on three measures: the percent of total manufactured product packaged, percent of the total packaged product that was shipped to sites, and the percent of product shipped that was dispensed. The results indicated that 67.8% of the product shipped to sites was dispensed to patients based on 12 companies and 57 studies (see Figure 6 on page 33).

Companies varied in their approaches to calculating supply overage. Nine of 12 companies calculated the percentage overage added into each study forecast; two in 12 used percentage added into aggregated study forecast; and one company calculated overage as a percentage of actual used (based on historical use).

Additional data in Figure 6 revealed more insights into organizations' attempts to manage waste or overage. As shown, 74% of packaged product was shipped to clinical sites and 90%

Error Rates: Product Impact Types

Type of Product Impact	Number of Studies with Impact
Error in shipping and handling (including temperature excursion)	19
Site mishandling	9
Customs Intervention	7
IVR Errors	7
Error in packaging	2
Error in labelling	2
Ambient	2
Controlled ambient	1
Other	1

Additional Product Impact

- Missing shipment
- Expiry update
- Resupply
- Retraining
- Regulatory Updates

N = 12 Companies, 57 Studies

Respondents selected multiple options

Source: Tufts CSDD

Figure 5. The effects of various reported clinical supply errors.

of manufactured or procured product was packaged. However, with the aforementioned 67.8% of product shipped and dispensed, this reflects challenges and opportunities in the alignment of clinical supply and clinical study operation execution.

Temperature excursion

The majority of respondents indicated that strategies did not differ between Europe and the U.S. for sourcing temperature maintenance products (e.g., shipping containers). Temperature monitoring strategies were primarily electronic. From the survey data gathered on temperature excursions occurring in transit were more frequent at customs clearance or at a site. The time taken to perform disposition of a shipment excursion was 57 hours, on average, with a range of six to 114 hours.

Factors impacting distribution

A number of other factors impact distribution, creating additional challenges for clinical supply executives. One challenge is the delay caused by obtaining import licenses—and the top countries listed were Argentina, Russia, China, Colombia and India.

Company approaches varied regarding the use of expiry dates. They were split on this issue, with five companies indicating their approach varied and six saying it did not. In addition, 11 companies indicated that they allow different expiry or "use-by" dates at different levels of the distribution chain; four reported they did not. Another area where companies had mixed approaches was regarding consistency in putting expiry dates on the shipping package. Nine organizations indicated they put expiry dates on a shipping package while seven revealed they did not. The primary methods for managing expiry date updates were to perform extension labelling at the site or to return to a depot to conduct it.

> It is acknowledged that waste varies by study, but the amount of overage impacts both cost and efficiency of supply.

Challenges in managing returns of drugs and supplies are also evident in a few key areas, including reconciliation and document destruction, complexity of managing returns and regulatory requirements. Managing returns varied across companies and could be destroyed at a site, returned to a local depot by region or country or returned to a central location.

Key performance indicators of distribution success were on-time shipments, percent of shipments with temperature excursions, percent minor deviations and on-time release or product released for use at a site (see Figure 7 on facing page). Other indicators used were percent major deviations and on-time receipt of shipments.

Companies were split on use of pooled supplies, with nine reporting that they used pooled supplies, while seven did not. The top challenge to using pooled supplies is the regulatory variation in acceptance across countries. No companies report using e-labelling, as regulations regarding its usage were expected to be clarified in the middle of this year.

Product Waste/Overage

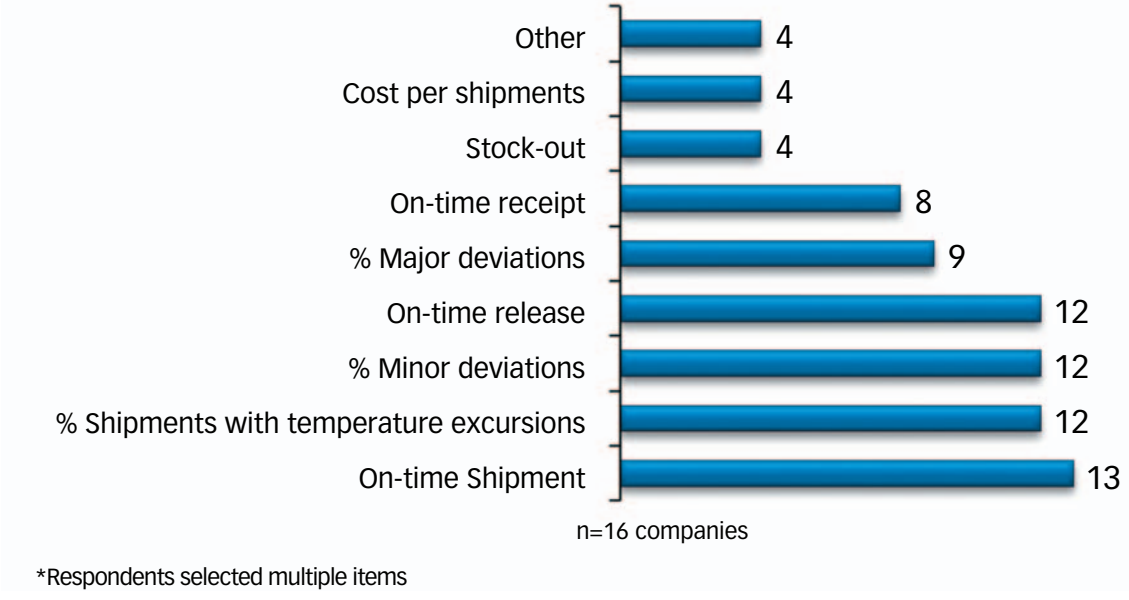
	Mean	Standard Deviation	CoV	Minimum	Maximum	Median	Range
Percent of Total Manufactured Product **Packaged**	89.9%	10.1%	.1	70%	100%	90%	30%
Percent of Total Packaged Product that was **Shipped to Sites**	74.1%	21.0%	.3	19%	100%	80%	81%
Percent of Product Shipped that was **Dispensed**	67.8%	24.5%	.4	5%	90%	80%	85%

N = 12 Companies, 57 Studies

Source: Tufts CSDD

Figure 6. Company calculation of supply overages across three measures.

Scorecard: Distribution Performance



Source: Tufts CSDD

Figure 7. Key performance indicators of distribution success.

Conclusion

The results of this study reveal that a great number of supplies are shipped across the globe. Of 73 global clinical studies reaching 5,682 sites, there were, on average 1,538 mean shipments. Companies used a mixed approach of centralized, local and regional strategies for shipments. Shipping times to investigative sites took an average of 3.4 days, with a coefficient of variation of 1.4, indicating disparities among shipping times to global sites (Figure 6).

Our findings for product impact and overage can help identify areas for continued improvement regarding cost and quality issues within clinical supply. Of the 57 studies further analyzed, there were 19 errors in shipping and handling and nine with site mishandling. This result represented 3% of studies and can be examined in further detail. Within the shipping and handling category, errors with temperature excursion were included. Any clinical supply logistic error rate may translate to potential site stock-out or product quality impact of the treatment that study subjects are waiting for. Companies can potentially look more closely into errors with product impact to see if there are strategies that can be implemented either within organizations or at the site level to reduce such instances. It is also critical for companies to achieve a balance between the risks and costs to optimize the clinical supply chain and increase quality. While cost containment is a priority, reducing inefficiencies in the supply chain is an ongoing challenge.

The results of this study indicate that two-thirds of all product shipped to sites was actually dispensed to patients. This result is considered typical given anecdotal evidence, with some organizations potentially having higher rates of overage as suggested by published data on this topic.[11] Coverage for geographic spread is another factor. It is acknowledged that waste varies by study, but the amount of overage impacts both cost and efficiency of supply. In addition, there is a relationship between clinical supply availability and the success of a study. A number of other factors such as cross-collaboration with clinical operations and other functions should be considered, especially those that manage the security of the supply. Companies may need to increase their "safety" stocks to address all the risks and potential scenarios that may occur.

Cross-collaboration also plays a role in the distribution strategy that an organization adopts. The studies we analyzed were split among centralized, local and regional strategies. Strategies varied across studies and by organization, perhaps due to the wide fragmentation and varied infrastructure of the global markets involved, but also due to unique company practices, set-up and strategies. It would require further study to examine what the drivers are for implementation of specific strategies and how best to optimize their usage. Nearly 60% of the trials we examined utilized outsourced logistics in managing the clinical supply chain, indicating that coordination among partners and vendors is also an important part of managing costs and efficiencies.

Forecasting supply can be linked to use of technology. Being able to forecast supply and the impact of factors such as enrollment, site selection and productivity and country selection is critical. Compared to 10 years ago, IRT plays a larger role in various clinical supply processes, from drug ordering and randomization to data extension management and drug reconciliation. Companies in our study estimated that nearly 70% of their studies are using IRT systems. The use of IRT is also evolving and taking on new functionality and standard platforms, as well as being integrated with other systems. Necessity and dependence of IRT becomes ever more critical to meet today's clinical study complexity, improve study efficiency and enhance compliance. Many organizations have already implemented cross-functional IRT governance teams to align processes within the organization and with vendors.

The results of this study provide a useful set of baseline measures for clinical supply professionals. The major findings also suggest an even greater need for upfront planning, risk mitigation, reducing waste, increasing efficiency and promoting cross-collaboration among those managing or involved with drug supply. In addition, there may be missed opportunities for cost savings by reexamining approaches to overage. There are also potential opportunities to improve the quality of product impact during shipping and handling. Furthermore, the relationship of clinical study efficiency with clinical supply logistics shall be studied by identifying and correlating the key strategy designs and key performance indicators.

References

1. Getz KA, Brown C. High turnover, protocol noncompliance plague the global site landscape. Tufts Center for the Study of Drug Development Impact Report, 17(1) 1-3 (January/February 2015).
2. Eighth UPS Pain in the Supply Chain Healthcare Survey. https://www.ups.com/media/en/UPS-PITC-Executive-Summary-North-America.pdf
3. Survey: Supply chain execs to up clinical trial logistics spend. *Outsourcing Pharma*. http://www.outsourcing-pharma.com/Clinical-Development/Survey-Supply-chain-execs-to-up-clinical-trial-logistics-spend
4. Getz KA, Kim J, Stergiopoulos S, Kaitin KI. New governance mechanisms to optimize protocol design. *Therapeutic Innovation & Regulatory Science*, 47(6) 651-655 (2013).
5. Getz KA, Stergiopoulos S, Marlborough M, Whitehill J, Curran M, Kaitin KI. Quantifying the magnitude and cost of collecting extraneous protocol data. *American Journal of Therapeutics*, 22(2) 117-124 (2015).
6. Lamberti MJ, Costello M, and Getz K. Global Supply Chain Management. From tactical to strategic: Tracking the evolution of global clinical supply chain management. *Applied Clinical Trials*. 21 (8) 2-6 (2012).
7. Clinical Trials – Regulation EU 5 November 2013. http://ec.europa.eu/health/files/eudralex/vol-1/2013_c343_01/2013_c343_01_en.pdf
8. Mcharg J. Ensuring the Integrity of Temperature-Sensitive Drugs along the Cold Chain, Pharma's Almanac, Global Pharmaceutical Supply Chain Trends Q4 2015 edition, (A Nice Insight Supplement), 2-48 (2015).
9. EMA Delivery time frame for the EU portal and EU database. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199078.pdf
10. Brown D. Trends in Contract Pharma Serialization and Supply Chain Security. *Contract Pharma*, 17(7) 62-63 (2015).
11. Lamberti MJ, Walsh T, Getz KA. Tracking trial cost drivers: the impact of comparator drugs and co-therapies. *Pharmaceutical Executive*. 33(5) 34-37 (2013). http://images2.advanstar.com/PixelMags/pharma-executive/digitaledition/05-2013.html#38

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6 Ways to Protect the Blind in Clinical Trials

Leon Wyszkowski, Steven Yoder, Susan Diehl

An overview of clinical supply blinding methods in the context of the current research environment.

Clinical supply professionals are on the front lines of protecting one of the most important aspects of clinical trial conduct—the blind. The terms "blinding" or "masking" in a clinical trial refer to the experimental method of keeping certain participants unaware of specific treatment assignments.[1] When conducted successfully, blinding can reduce bias in randomized trials. However, study integrity may be at risk if the blind is broken unintentionally.

At its most basic level, the concept of blinding appears simple, but in reality there are many practical considerations that add several degrees of difficulty.[2] In recent years, this level of complexity has increased with protocol design advances and more people involved in supporting clinical studies. The need for blinding has grown within some medical specialties such as oncology, where early phase researchers are looking beyond safety studies toward evaluation of efficacy, which may require blinding of clinical supplies.[3]

Today, there is greater electronic risk of releasing sensitive, unblinded, information to trial personnel who are supposed to be blinded. Adding new challenges for clinical supply operations are new research methods such as adaptive design, which can introduce changes in treatment assignment after an interim analysis.

Despite the high burden of risk placed on clinical supply professionals, there are limited training resources and literature available on this topic.[4] While most organizations provide basic instruction about the need for blinding, clinical supply managers are often forced to learn about it the hard way when unintentional unblinding happens on their watch.

In light of these challenges, the authors identified six ways that supply chain professionals can help protect the blind in clinical trials. Since the promise of adaptive design has captured the attention of many clinical researchers, we address its implications before more general considerations. We begin with our recommended priority list:

1. Participate early in design planning for adaptive trials
2. Ensure proper technology configuration for adaptive trials
3. Consider all five human senses
4. Build a blinding procedures checklist using the protocol
5. Stay vigilant during administrative tasks
6. Reinforce initial responsibilities

Our first suggestion for protecting the blind comes as adaptive design made news. In May 2015, the U.S. FDA issued guidance extending its recommendations to adaptive medical device trials.[5] Five years ago, the agency issued its guidance for adaptive drug studies. These guidance documents offer helpful information for clinical supply professionals as they consider tip one.

Participate early in design planning for adaptive trials

An adaptive trial is a multi-stage study that uses accumulating data to modify trial conduct without compromising integrity. Modification plans are

established in study design and triggered when an interim analysis shows that adapting the trial may improve efficiency. Many pharmaceutical companies have successfully adopted this method across their clinical developmental portfolios. For instance, Merck & Co. reported in 2011 that it introduced adaptive design for 40% of its late-stage clinical trials and saved over $200 million as a result.[6]

When adaptive trials are in the design stage, clinical supply professionals can help establish procedures for responding to those changes that would have the highest operational impact. It will be important to prepare the blinding strategy for the following adaptive events:

- Sample size adjustments
- Modified randomization to drop or add treatment arms or doses
- Re-randomization of the same patients
- Changes to the allocation ratio or treatment assignment probabilities
- Stopping early due to success or predicted failure

If clinical supply professionals bring strategy considerations to the table early, it may help shape the proposed adaptations so they include workable measures that prevent accidental unblinding. Note that there may be additional challenges because adaptive designs are typically used early in development when drug supplies are hard to come by or difficult to manage due to unconfirmed stability.

As the FDA stated in its draft guidance on adaptive design in drug trials, "protecting the study blind is particularly important to avoid the introduction of bias in the study conduct and to maintain confidence in the validity of the study's results." A sound clinical supply strategy is essential to ensuring this protection remains robust while the trial conduct changes in response to clinical results.

Ensure proper technology configuration for adaptive trials

Interactive response technology (IRT), also known as interactive voice or web response systems (IVRS/IWRS), usually plays a large role in designing and controlling adaptive trials so that randomization, the supply chain, and blinding strategy remain robust and protected. Preparing an adaptive design without adequate technology is not recommended, especially in larger trials.

If a study sponsor does not have this technology in place, clinical supply professionals are well placed to help select the appropriate software. Once the technology is installed, a biostatistician—often working with the clinical trials team—can ensure it is configured properly with features such as the ability to turn on or off treatment arms within one schedule (a randomization list or drug packaging list). Adaptive trials often call for creative ways of using IRT to improve clinical supply forecasting, supply strategy adjustment, expiry date management, and study medication blinding maintenance. An experienced clinical supply manager has the ability to respond to this complexity by:

- Providing input into the configuration of the drug packaging list
- Participating in the communication of batch releases that must be recognized in the IRT

> **While most organizations provide basic instruction about the need for blinding, clinical supply managers are often forced to learn about it the hard way when unintentional unblinding happens on their watch.**

- Ensuring the process for shipping of materials is established and followed based on orders sent by the IRT to the depots
- Providing input or authorization to the overall materials being managed by the IRT
- Ensuring the naming and unitization elements align with the physical nature of the materials

Consider all five human senses

In both adaptive design and traditional study design, clinical supply teams can work in tandem with formulation experts to ensure the test articles have matching physical attributes. When reviewing designs for these products, remember to consider all five human senses. The requirement for matching must go beyond the actual product characteristics and extends to all associated packaging and labeling.

The original manufacturer's stability data usually supports only the medicine in its original packaging. Unless equivalent or more protective packaging is used, which itself may be difficult to determine, a reduction in the medicine expiry date may be unavoidable.[2]

During a recent online forum about blinding clinical supplies, several questions were introduced by the audience about matching physical properties of investigational drugs to placebos or comparators.[7] The attendees were especially concerned about masking the visual identity of liquid presented in syringes.

One proposed solution is the use of polyethylene soft shells that obscure the color and cloudiness of some liquids. Another person in attendance noted the complications of matching product taste in liquid formulations. Compared with tablets and capsules, the sensory characteristics of taste and smell are more pronounced and more challenging to duplicate. This issue of blinding liquids comes up frequently in pediatric clinical trials that rely on these dosage forms to ease administration.

The relative importance of the sensory evaluation depends on the route of administration and the dosage form. When it comes to blinding capsules, for instance, a simple solution such as over-encapsulation will usually provide sufficient masking. But the same can't be said of injectable therapies

where the viscosity of the study drug differs substantially from the placebo, or inhalants with slightly different odors. In all cases, it makes sense to understand how perceptions of the test articles are influenced by shape, size, color, texture, weight, taste, and smell.

Build a blinding procedures checklist using the protocol

Though they can be involved early in the trial design, in many cases, clinical supply professionals have most of the protocol delivered to them in final form from their clinical colleagues. With this document in hand, it may pay dividends to build a simple blinding procedures checklist for clinical supplies. The one-page checklist makes it easier to recall specific details from among the many trials that are often running concurrently. The form can start with blank fields for the protocol number and title, followed by name and contact information for the relevant project manager.

Open checkboxes on the page enable a supply team member to select the protocol design type (open label, single blind, double blind or triple blind), the trial personnel who will remain blinded and unblinded to treatment assignments (client/sponsor, project manager, investigators, study coordinators, monitors, analysts, etc.), and the randomization system. At the end of the page, include blank fields with name, affiliation, address, and phone number to identify the contact people to notify in case of an emergency unblinding, and those who have the authority to unmask the study results.

Beyond items used in the blinding checklist, the protocol should provide more details about the method of blinding—for instance over-encapsulation for capsules and tables, or the soft shells described above for syringes and vials. It can also discuss the similarity of treatments based on appearance, taste, or other characteristics. And finally, it will give full instructions for unblinding the study treatment if an emergency dictates a break in the blind is warranted.

Stay vigilant during administrative tasks

As noted, email and other electronic communications among trial personnel can inadvertently reveal treatment allocation. These communications include both written text and attachments (randomizations and print run reports showing ranges with treatment groups, batch documentation showing what is being packaged with ranges, packing and return lists, invoices, shipping documents, etc.). In some cases, exclusive details are benign, but when coupled with a second exclusive detail they lead to full or partial unblinding.

With the proliferation of email, web portals, instant messaging and other electronic communication channels, it is harder today to stay vigilant during administrative tasks that often become routine. Before sending a message, it always makes sense to ask recipients if they are blinded to the study information. If they are, ask for an individual who is unblinded and can provide the approvals or have the documentation blinded before forwarding it to the preferred contact.

> **While bias tending to favor new drugs is inherent in every trial, clinical supply teams that help establish and support a blinding strategy will know they have done their best to minimize it.**

Too often what gets transmitted are unique sequence numbers associated with each material unit of active drug and placebos. These numbers would not appear on the label, but are used in site shipment requests. As the name suggests, the numbers are provided sequentially and grouped based on the drug type (active might be sequence numbers 1-10 and placebo might be sequence numbers 11-20, for example). This makes it easier to pull and box supplies. But if these numbers were learned, it is possible to group or deduce the drug type, if provided additional reference information.

Limit access to these numbers to the unblinded personnel who use the codes to reassign treatments when necessary, such as after an interim analysis in an adaptive trial.

It's also important that the sequence numbers themselves can't be traced. Study volunteers may be able to identify their assignment based on mild side effects such as flushing of the face or a metallic taste in the mouth. If several volunteers with similar numbers experience the same side effect it could compromise the blind.

Other potential unblinding hazards are misaligning the label on medication kits, variance in label text, color or print style, different carton substrates, carton assembly, and tampers seals placed differently.

Apart from email, other electronic information sharing presents unblinding risk. For example, granting inappropriate access to secure content in a web portal may give blinded trial personnel details about the end product and, therefore, the potential to break the blind.

Shipping documentation, both in electronic and hard copy format, presents another administrative pitfall, especially for trials that share drug supplies across multiple protocols. Historically, customs officials need to know what is in the shipping container and it is commonly stated on the packing list or commercial invoice. In the case of supply sharing or "pooling," the packing list would show "Material Pooled" with the material or randomized numbers listed, items for Protocol XYZ and an associated invoice that would list X product of active or placebo with a unit cost and the subtotal.

Reinforce initial responsibilities

Accidental unblinding may also happen when a distribution center fails to remove all the drug identification packing slips

from shipping cartons, or if a laboratory doing sample analysis mistakenly sends the investigators results sorted by treatment type. This brings up the importance of reinforcing initial responsibilities throughout the clinical supply chain.

As noted, clinical trial conduct is often a team effort that spans many time zones, countries, languages, and organizations. Setting appropriate management practices is as important as reinforcing them throughout the trial.

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Part of this initial planning is the design of a strategy for unblinding, in case of an emergency, as noted earlier. Established in the protocol, methods for fast and efficient unblinding can include tear off strips that are removed from the packaging and stored in the site pharmacy for emergency access. IRT systems, when used, provide the immediate access for emergency unblindings to be performed. The IRT will communicate the patients treatment assignment. Access to such a transaction would be controlled by user role and any protocol-specific conditions that must be met in order to unblind a patient. Clear instructions and lines of communications will help ensure proper use of these emergency procedures.

In closing, these are just a few steps that clinical supply professionals can take to protect the blind and prevent bias. The impact of bias on the evaluation of treatment effect is difficult to assess, but it has been estimated that the absence of double-blinding exaggerates treatment effects by 14% as compared with double-blind trials.[8] While bias tending to favor new drugs is inherent in every trial, clinical supply teams that help establish and support a blinding strategy will know they have done their best to minimize it.

Clinical trial conduct is often a team effort that spans many time zones, countries, languages, and organizations. Setting appropriate management practices is as important as reinforcing them throughout the trial.

References

1. Wang D, Bakhai A. Clinical Trials: A Practical Guide to Design, Analysis, and Reporting. Remedica, 2006, 480 pages.
2. Wan M, Orlu-Gul M, Legay H, Tuleo C. Blinding in pharmacological trials: the devil is in the details, *Archives of Disease in Childhood*, Sept 2013; 98: 656 - 659.
3. Percy Ivy S, Siu LL, Garrett-Mayer E, Rubinstein L. Approaches to Phase 1 Clinical Trial Design Focused on Safety, Efficiency, and Selected Patient Populations: A Report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. *Clinical Cancer Research* 2010; 16:1726-1736.
4. Cook S, Yoder S, Owings C, Campbell B, Gentile C. The Blinding of Materials in Clinical Trials: Essential Processes for Ensuring the Integrity of Clinical Study Data. *Pharmaceutical Engineering*, January/February 2014, Vol. 34 No. 1.
5. Adaptive Designs for Medical Device Clinical Studies, Draft Guidance for Industry and Food and Drug Administration Staff. Food and Drug Administration Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, May 18, 2015.
6. He W, et al. Practical Considerations and Strategies for Executing Adaptive Clinical Trials. *Drug Information Journal*, 2012; 46(2) 160-174.
7. Diehl S, How to avoid breaking the blind in clinical trials. Xtalks Webinar, March 18, 2015. http://xtalks.com/blinding-in-clinical-trials.ashx. Accessed June 9, 2015.
8. Casteels M, Flamion B. Open-label trials and drug registration: a European regulator's view. *Journal of Thrombosis and Haemostasis*, 2008; 6:232–4.

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Varied Needs for Biological Sample Management

Eric Hayashi

From basic blood draws to more involved samples, keeping accurate track and records is crucial for trials.

Although it's difficult now to remember a time before computers were readily available, prior to the 1970s, the tracking of biological samples and their annotations was tedious, time-consuming and error prone. The growing presence of affordable computers and the desire to streamline the collection and reporting of data led some laboratories to develop their own management systems, while others saw profit in developing them for commercialization. Today, sample management systems range from manual processes aided by spreadsheets to sophisticated services that accession samples at the point of collection and track them and their unique data all the way into the biorepository

What has changed between the earliest systems and today is that biological samples have become exceptionally more valuable. Samples that were once tested and discarded are often carefully preserved in biorepositories as insurance against future regulatory inquiries, as well as to potentially serve as vital keys to some yet-unknown branch of research. With such valuable assets at stake, it is important to ensure that each and every sample from every clinical trial—untold billions in all—is known and that its entire history can be verified from the moment the sample is collected until it is deemed no longer needed.

A clinical laboratory sample management system should have the following features:

- **Accessioning**, where a sample is assigned a unique identity attached to attendant demographic data, either at the time of collection or upon entry into the laboratory environment
- **Anonymization**, to protect the privacy of individuals
- **Tracking**, which may include logistical tracking and tracking within the analytical workflow of the lab
- **Quality control** of attendant processes
- **Analysis and storage** of collected data
- **Storage or dispensation** of the physical sample

This article examines the key components in various sample management systems and relates them to the research type for which they are being used. This comprises simple testing and storage within the same lab setting, to complex protocols encompassing multiple sites in foreign and rural locations, as well as detailed cryologistics, chain of custody requirements and long-term biostorage.

Beyond spreadsheets: LIMS

When the needs of a laboratory grow beyond spreadsheets and off-the-shelf solutions, many initially turn to a laboratory information management system, or LIMS. Once prohibitively expensive, simple LIMS and software as a service (SaaS) systems are within reach of even small and virtual organizations.

At a basic level, a LIMS can be any piece of software that manages the information that is produced or digested in a laboratory setting. Although there may be a few foundational requirements that seem to apply across all laboratory types, such as the ability to track and manage samples, the variation of one LIMS to the next may be dramatic.[1] Most LIMS start from the premise that a process exists, e.g., samples are received, accessioned, bar-coded, processed according to protocol, data analyzed and stored in a freezer. A different lab may follow a different process, and one of the defining differences between LIMS choices is the degree of flexibility in making the LIMS follow your processes or vice versa.

The core function of LIMS has traditionally been the management of samples. This typically is initi-

ated when a sample is received in the laboratory, at which point the sample will be registered in the LIMS. The registration process usually involves accessioning the sample along with clinical or phenotypic information and producing bar codes to affix to the sample container. The LIMS then tracks chain of custody as well as sample location, typically a particular freezer location.

Benefits from implementing a LIMS can be both qualitative and quantitative, but are very dependent on the lab environment. In a pharmaceutical quality assurance lab, for example, quantitative benefits may include increased efficiency through integration of systems, automation of routine reports, and streamlining the review process. In a research laboratory, the benefits may be more about adaptable experiment design and workflow. In both instances, however, qualitative benefits would include reduction of transcription error, adherence to regulatory requirements and easy accessibility to data.[2]

Modern LIMS have extensive configurability, enabling them to adapt to individual laboratory environments. LIMS users may also have regulatory concerns to comply with such as CLIA, HIPAA, GLP, and FDA specifications, affecting certain aspects of sample management. One key to compliance with many of these standards is audit logging of all changes to LIMS data; in some cases, a full electronic signature system is required for rigorous tracking of field-level changes to LIMS data.[3]

In addition to configurable fields for special processes, LIMS capabilities typically include:

- Audit management
- Bar code handling
- Chain of custody
- Compliance tracking
- Configurable annotation
- Document management
- Electronic data entry and transfer
- Instrument calibration and maintenance
- Inventory and equipment management
- Process management
- Personnel and workload management
- Quality assurance and control
- Reporting
- Search
- Workflows

LIMS platforms

Whether part of a LIMS or as a standalone sample management system, deployment of the application can be on one of several different platforms.

A thick-client system typically has part of the software residing on the user's computer or workstation, where the processing takes place, with the remainder installed on the user company's servers that take care of data storage. Because the program is resident on computers within the user company, changes, upgrades and other modifications must of necessity happen on the client side. Thick-client systems have some advantage of speed, but require a robust computing environment and can only be accessed by those with network access. Pricing is typically based on an initial purchase covering a set number of licenses and ongoing technical support.

A thin-client, or SaaS system, offers functionality through a web browser. The software resides on a host server that processes information without saving it to the user's hard drive. Upgrades and other modifications are handled by the hosting company, and the user's only responsibility is maintenance of the integrity of the web browser. Advantages to a thin-client system include significantly lower cost of ownership and fewer network and client-side maintenance expenses, making it attractive to small and medium-sized laboratory enterprises. Disadvantages of SaaS include a need for increased network throughput, and some compromises in configurability and functionality. Pricing is typically based on licensing fees for each user on the system plus ongoing support.

A web-based architecture is a hybrid of the thick- and thin-client architectures. While much of the client-side work is done through a web browser, the system may also require the support of desktop software installed on the client device. Web-based architecture has the advantage of providing more functionality through a more user-friendly web interface.

Beyond LIMS: Central laboratories

When the needs of development teams grow beyond what their own local lab can handle, they may contract with a central laboratory to handle sample management along with a wide range of associated services.

According to Dr. Francisco Leão, Jr., writing in *Applied Clinical Trials*,[4] the central laboratory concept was developed in the early 1990s by laboratories delivering services to major pharmaceutical companies:

"The goal was to consolidate the test results and data originating in different clinical sites, which was previously analyzed in local labs. Bringing the samples to one single laboratory would avoid consolidation of biased test results among different laboratories, all of which could be using different analytical platforms, kits, and reference values. This concept was first applied to clinical studies conducted in the United States. Soon after, the courier industry started offering solutions for biologic sample transportation, which allowed the central lab concept to be applied globally. Later, the concept of the affiliated laboratory was created. The affiliated laboratory covered geographic regions that had difficulties exporting biologic samples. As a consequence, the central laboratory became more global and started to build different types of associations with analytical laboratories in different parts of the world."

A central lab is exclusively responsible for lab assessments and provides services from conducting lab tests and compiling lab test reports, to contracting courier services for delivering lab kits and biosamples to and from investigative sites.

Affiliated central labs enable large multi-country studies—even complex genomic or adaptive protocol trials—by ensuring

compliant aggregation of the data. But it's not necessarily easy. As Dr. Leão, pointed out, clinical site staff may be responsible for logistical tasks, causing samples to reach the lab in a condition that doesn't allow them to be properly analyzed. There are also difficulties in shipping lab materials to remote sites in developing countries that raise costs and cause logistic constraints. While query resolution and clinical site support processes are usually best dealt with by local teams and staff, Dr. Leão warns that differences in language and time zones between central labs and clinical sites may be problematic. The key to running successful global studies through affiliated central labs is harmonization.

Harmonization is a process that must be carried out by affiliated central labs in order to integrate results of biological sample tests from different laboratories, and avoid any possible bias generated by technical differences among them. Depending on the degree and method of harmonization that a group of labs implements, the labs may reach a very close technical comparability and be considered a single entity by the trial sponsor, delivering the same service and results all over the world. Of course, there are different aspects and levels of harmonization.

Analytical platform harmonization. Analytical equipment, methodologies, kits, and reagents used in the laboratory test either in general or for the specific trial are compared and, if necessary, addressed through correlation tests. These can show that the results coming from different equipment can be considered homogeneous and, therefore, can be consolidated in the study databank. Also to be considered is the IT platform, because the final product is the data, which will have to be generated, transmitted and stored in ways compatible and compliant within the study database.

Reference value harmonization. Although important for the data analysis and data management process, this can be challenging, depending on the population and tests involved. Safety test reference values are easily harmonized because most of them follow international standards, but more esoteric testing requires a higher level of scrutiny.

Certification, accreditation and external QC programs. Laboratories involved in the same study are typically harmonized according to their national and international certification and accreditation.

Laboratory routines and reports. To ensure harmonization, laboratory routines, not just the equipment, should go through a harmonization process. Calibration frequencies, preventive equipment maintenance and repeat thresholds should be comparable among participating laboratories.

Beyond central labs: Sample management as a service

Although central laboratories are able to network together to provide services, sample tracking is not necessarily the highest priority. For the most part, samples are not accessioned into the system until they reach the lab and are entered into the networked LIMS or clinical trial management system.

For high-value samples, especially those being obtained in developing regions of the world, some companies provide sample management as a service that begins with a detailed sample management plan to help control pre-analytic variables that could compromise sample integrity or otherwise alter research outcomes. The planning procedure looks at every detail, including what samples should be collected, how they should be handled and how they will be accessioned into a sample tracking system, as well as how they will be transported, analyzed and prepared for long-term storage. Under this scenario, every step in a sample's life cycle is monitored, recorded and carried out through adherence to uniform standard operating procedures that are harmonized throughout the trial. From collection through cold chain transport, to central lab testing and biorepositories, everything must be standardized: collection tubes and shipping containers; laboratory equipment; and cryogenic freezers.

Specific considerations

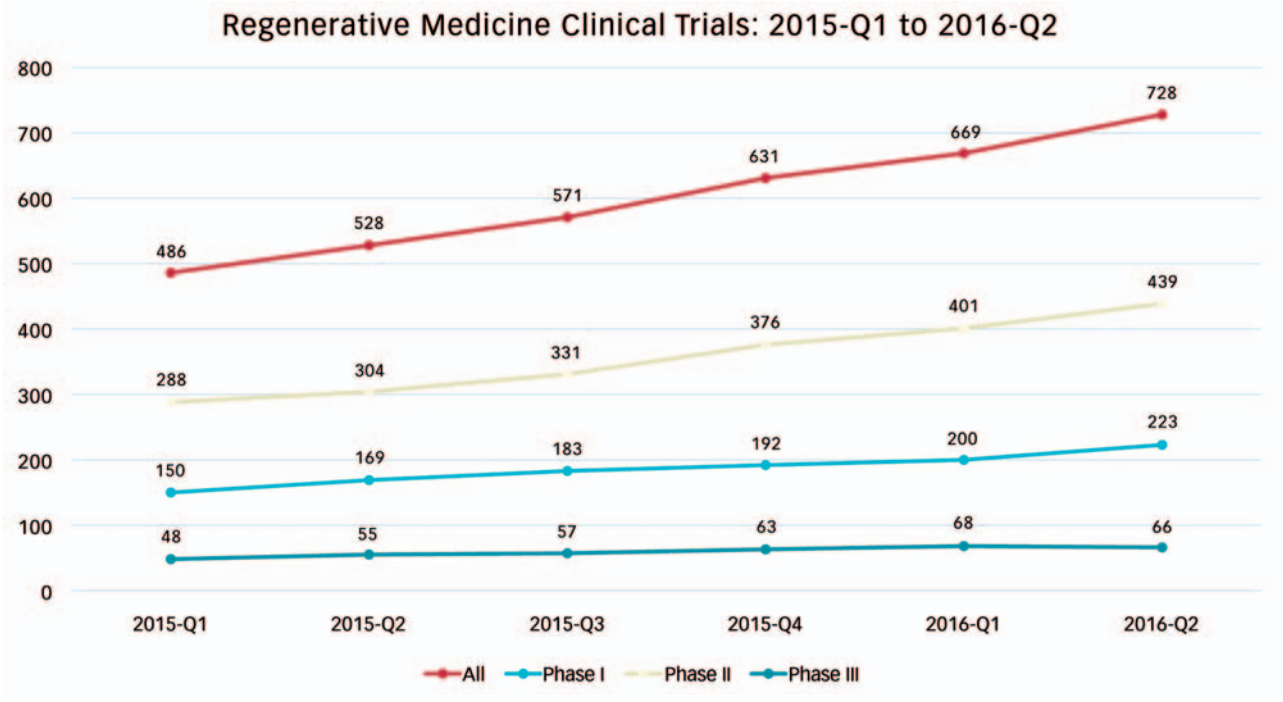
When preparing a comprehensive sample management plan, sponsors should vet their providers to ensure they have the regional capability and capacity to carry out the program logistics. More remote regions, for example, will require the use of advanced dry vapor shipping dewars designed to minimize the risks of temperature excursions, with hold capacities of <-150° for up to 10 days. Before the study begins, the investigator site list should be evaluated to determine if specific locations should be subject to a logistics dry run, enabling the development of alternative logistics solutions.

Another aspect to be considered is providing sites with appropriate tools. If the protocol calls for collecting blood and isolating peripheral blood mononuclear cells (PBMCs), each of the sites must have kits containing the right kind of collection tubes, labeling and bar-coding equipment as well as shipping containers that have been certified for a variety of conditions, including crush resistance and temperature maintenance.

Because researchers are looking for the best ways to leverage individual specimens to drive clinical research as well as translational and personalized medicine, they want complete datasets surrounding each specific sample. Unlike LIMS or many central labs, a critical aspect of high-end sample management is accessioning samples at the time of collection, using a digital pen for compliance, and condition monitoring systems to record sample status at each stage. This enables individual samples to be tracked and monitored from collection through testing and during long-term storage and also provides a 21 CFR Part 11 compliant audit trail for later reference.

New cellular and gene-based research and studies on immunology or cancer immunotherapies require additional care in sample management. With each study participant sample collected at different intervals during the study, the biorepository may, for example, be required to extract DNA and RNA and make aliquots of each sample, or isolate PBMCs and cryopreserve them in liquid nitrogen. How development teams pre-

New Challenges for Sample Management



Source: Alliance for Regenerative Medicine quarterly reports

Figure 1. New cellular and gene-based research and studies on regenerative medicines and immunotherapies require additional care in sample management. Regenerative medicine, in particular, is an area experiencing a significant increase in the number and complexity of clinical trials, and thus a greater need for careful planning, standardized procedures and the use of a comprehensive sample management system.

serve the sample for downstream testing becomes increasingly important as we move closer to translational medicine and to expedite drug discovery for personal medicine and companion diagnostics utilizing biomarkers. As a facet of sample management planning, teams must imagine every possible use for samples as a part of the protocol development discussion.

Conclusion

As technology develops in each of these areas—collection tools, cryogenic logistics, condition monitoring, IT integration, biostorage—it is likely that a greater percentage of samples will be treated with more care and attention to their long-term viability and usefulness. In the meantime, even relatively simple systems can maintain the integrity required for most clinical and post-clinical applications.

Sample management runs the gamut from very rudimentary standalone systems, to sophisticated LIMS, to large central labs managed by pharmaceutical companies or CROs. Any one of these may be perfectly appropriate, depending on the size, scope and strategy of the development program. Routine assays and safety testing require only modest management, but as the focus of research shifts to preserving the integrity of scientific assets to support biomarker discovery projects, personalized medicine efforts and the development of other, yet-to-be-determined, genomic-based treatments, the value of each individual sample takes on a greater importance and greater value. In these cases, implementation of a robust sample storage management system, including a comprehensive sample plan, is necessary to ensure samples collected during clinical trials will benefit both current and future R&D efforts.

References

1. 2011 Laboratory Information Management: So what is a LIMS?, Sapio Sciences. July 28, 2010.
2. Joyce, John R., et al. Industry Insights: Examining the Risks, Benefits and Trade-offs of Today's LIMS, *Scientific Computing*, March 30, 2010. http://www.scientificcomputing.com/article/2010/03/industry-insights-examining-risks-benefits-and-trade-offs-today%E2%80%99s-lims
3. Kent, Thomas, Managing Samples and Their Storage, *Lab Manager*, May 13, 2009
4. Leão, Jr., Francisco. The Local Central Lab Model, *Applied Clinical Trials*, April 1, 2008

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Operational Challenges for Biosimilar Studies

Hazel Gorham, PhD, Rodeina Challand

Using strategic planning to address hurdles in biosimilar development programs from the outset.

A number of top-selling biological products in key therapeutic areas such as cancer, diabetes, and rheumatoid arthritis have recently lost, or will soon lose, patent protection. IMS Health estimates that $92 billion in global sales of branded drugs and biological products will have lost patent protection between 2011 and 2015.[1]

This "patent cliff," together with public healthcare budget cuts, advances in technology for the manufacturing of biologics, and the identification of specific legal and regulatory pathways in many countries for the approval of biosimilars, has fueled the race for the manufacturers of biosimilar products to obtain marketing approval for their products as quickly as possible.

Due to their complex structure and manufacturing processes, a biosimilar product is not an identical copy of the original reference product and its similarity to the reference must be demonstrated. The development of a biosimilar shares most of the operational challenges facing that of new chemical entity.

However, due to the specific regulatory requirements for demonstrating similarity across all phases, and the lack of understanding of the concept of biosimilarity among stakeholders including physicians and patients, there are a number of unique operational challenges specific for biosimilar development.

This article explores some of these challenges and how they can be addressed from the outset with strategic planning.

Reference product

As is required of manufacturers of originator or reference products, manufacturers of biosimilars must demonstrate the quality, efficacy, and safety of their product. However, regulatory approval of a biosimilar product is based on a demonstration of its similarity to the previously approved reference product, and not on an independent demonstration of its efficacy, safety, and other characteristics (see Figure 1 on facing page).

Demonstration of similarity to the reference product starts at the beginning of development, when the characteristics of the biosimilar product are first established. A key aspect of a direct comparative analysis of the biosimilar to the reference drug is to determine the inherent variability of the reference product's critical quality attributes (see Figure 2 on page 46),[2] including changes in these attributes due to modifications of manufacturing processes (see Figure 3 on page 47).[3,4] The European Medicines Agency (EMA) guideline refers to this as determining the quality target product profile, or QTPP.[5,6]

The ranges for each critical quality attribute need to be established when determining the target profile for the biosimilar product. To do this, the manufacturer of the biosimilar must procure multiple batches of the reference product with differing expiry dates. This can be problematic, as originator companies release only a limited number of batches of commercial

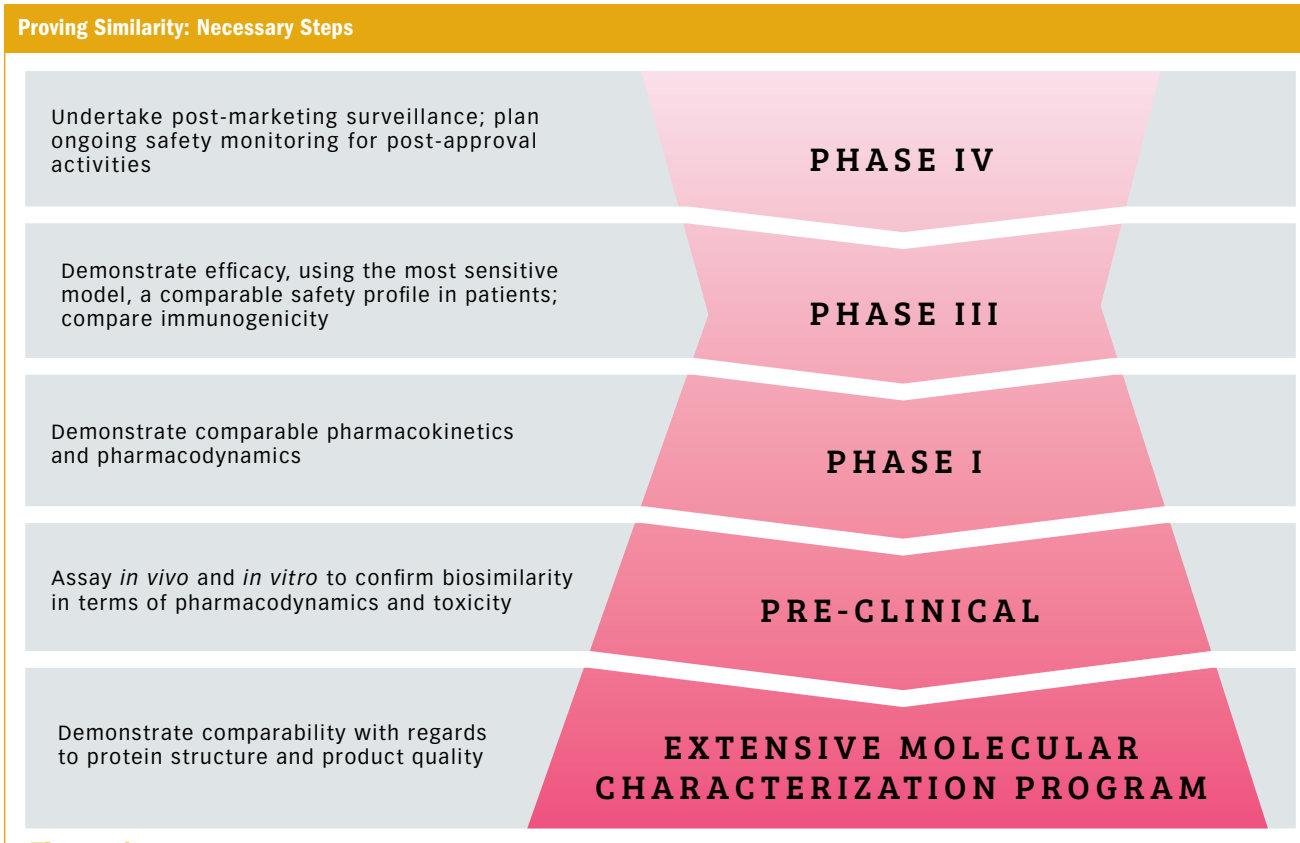


Figure 1. The European Medicines Agency's (EMA) development and approval pathway for biosimilars—a stepwise approach to demonstration of biosimilarity between a biosimilar and the originator reference product.

stock with different expiry dates over a given period of time. Therefore, it is critical that manufacturers of biosimilars take into account the need to acquire these multiple batches over a significant time period, including prior to the start of development and manufacturing activities, and throughout the development process.

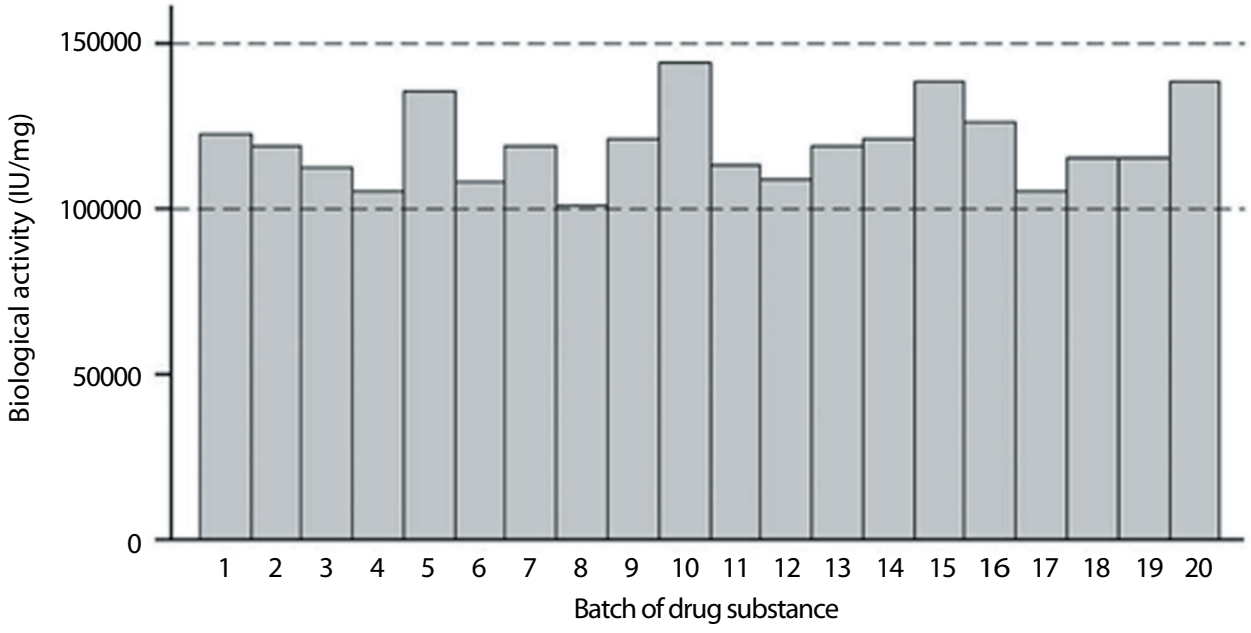
Comparative Phase I pharmacokinetics/pharmacodynamics (PK/PD) studies are an essential part of the biosimilar development program. Bioequivalence studies for biosimilar products are generally large in size due to large intra- and inter-subject variability, and can involve up to hundreds of subjects, depending on the molecule. Obtaining a sufficient quantity of a single batch of the reference product to conduct a large Phase I study can be challenging. Some variability between different batches of the reference drug can be expected (e.g., biological activity, Figure 2); however, such variability could compromise the comparability exercise and as such it is optimal to use only one batch in the PK/PD study.

If regulatory approval of the biosimilar product requires the conduct of comparative efficacy and safety studies, an even larger quantity of the reference treatment will need to be purchased. Although the use of multiple batches of reference product for these types of studies is acceptable, and even preferable, ensuring a continued supply of the drug is challenging as manufacturers of originator products carefully control the release of commercial supplies. Furthermore, the total cost for purchasing the reference product should also be taken into account, as it can be a significant part of the overall study budget.

> **Regulatory approval of a biosimilar product is based on a demonstration of its similarity to the previously approved reference product, and not on an independent demonstration of its efficacy, safety, and other characteristics.**

Both the reference drug and the agent under investigation are considered to be investigational medical products (IMPs) in comparative efficacy and safety studies. The release of an IMP by a qualified person and importation of

Quality Variability of Innovator Product



Source: Schneider C.K. (2013) "Biosimilars in Rheumatology: The Wind of Change." *Annals of the Rheumatic Diseases*, 272(3), pp. 315-317

Figure 2. An example of batch-to-batch variability in biological activity for a biologic drug substance. *In-vivo* biological activity of 20 consecutive batches of Binocrit.

the IMP into many countries may require a certificate of analysis (CoA). Obtaining a CoA for commercial supplies of reference product can prove difficult. In fact, supportive documentation for reference drug purchased from the US will not include a CoA.

If a CoA is not available, the biosimilar manufacturer will have to conduct its own analysis of the reference product to produce a CoA, which could have significant impact on timelines and cost.

Clinical Studies

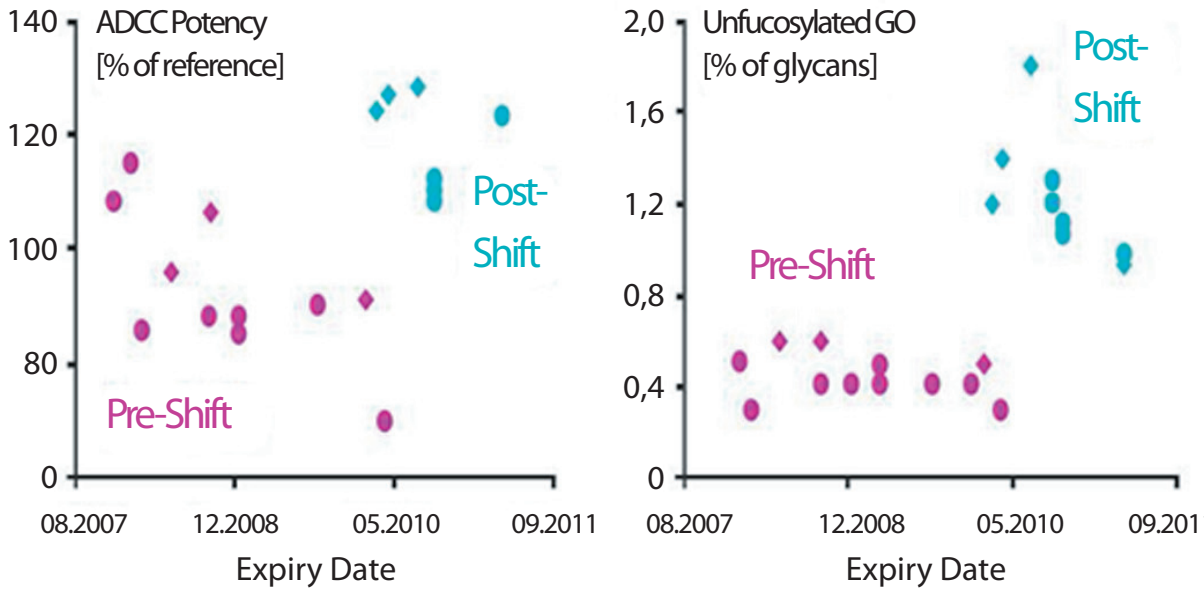
Phase I pharmacokinetic/pharmacodynamic challenges

Comparative PK studies are designed to demonstrate similar PK profile of the biosimilar and the reference medicinal product with regard to key PK parameters. The criterion used to compare two treatments with the purpose of evaluating if the 90% confidence interval of the geometric mean ratio of AUC and Cmax between the test and reference fall within 80%-125%.[7] The ideal study design to evaluate bioequivalence of two products is a crossover design (two-period, two-treatment crossover design), where the two phases of treatment are separated by a washout period. The washout period should be sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally, at least five elimination half-lives are necessary to achieve this.

The ideal study design to evaluate bioequivalence of two products is a crossover design, where the two phases of treatment are separated by a washout period.

The primary advantage of the crossover design is that since the treatments are compared on the same subject, the inter-subject variability does not contribute to the error variability of the study. However, concerning a product with a long half-life—a common characteristic of biosimilar products—a crossover study design would lead to protracted clinical studies. Such lengthy studies are susceptible to high subject dropout rates and increased subject variability, thereby potentially putting the successful outcome of the study at risk. Under such circumstances, regulatory guidance, from both the FDA and EMA, allow for a parallel study design.[8,9] In a parallel design, although there are no concerns with regard to sequence, period, or carryover effect or dropouts during the study, the inter-subject variability is very high and, hence, the sensitiv-

Manufacturing Modifications



Source: Schiestl M., et al. (2011) "Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals." *Nature Biotechnology*, 29, pp. 310–312

Figure 3. Comparison of a different pre- and post-change batches of Rituxan/Mabthera.

ity of the test considerably reduced. A larger number of subjects compared to a crossover design is, therefore, required to attain the same sensitivity.

The need for a large number of subjects, within a Phase I study setting, can be a point of concern for an ethics committee (EC). Careful explanation of the concept of biosimilarity, regulatory guidance for biosimilar product development, and justification for the proposed study design should be provided up front to the institutional review board (IRB)/EC to minimize the risk of a rejection of the clinical trial application. The recruitment of large number of subjects for a Phase I biosimilar study is particularly challenging. Recruitment of patients from multiple sites can significantly add to the variability of the patient data. Patients, therefore, should be recruited from a single site.

Phase III safety and efficacy study challenges

Efficacy trials of biosimilar medicinal products do not aim at demonstrating efficacy, per se, since this has already been established with the reference product. The aim of the clinical data is to determine that there are no clinically significant differences between the biosimilar and its reference product.

As for all clinical comparability trial designs, assay sensitivity defined as a "the ability to distinguish an effective treatment form a less effective or ineffective treatment"

Site support with regard to protocol training and supportive protocol study aids is key to obtaining quality data in biosimilar studies.

has to be ensured.[10] Assay sensitivity in a non-inferiority or equivalence trial is deduced from two determinations: 1) historical evidence of sensitivity to drug effect, and 2) appropriate trial conduct (i.e. trial conduct should also adhere closely to that of the historical trials and should be of high quality). Determining the drug effect size from historical reports and adhering to historical trial design can be problematic.[10] Patient treatment is continually evolving and with time, new treatments and regimens are accepted as the standard of care.

Different regimens are also often used in different countries for the same drug product, a particular challenge for the development of an acceptable global clinical study design. For example, the originator product Neulasta® (pegfilgrastim) clinical efficacy studies examined the duration of severe neutropenia in breast cancer patients undergoing chemotherapy treatment consisting of doxorubicin and docetaxel (AT).[11] However, the standard of care has changed over time with other chemotherapy

regimens, and this could lead to issues with ECs and investigators. Defining the effect size can also be challenging without historical data, which, in turn, could result in the study not being powered appropriately unless a placebo arm is included.

Additionally, the choice of clinical endpoints, selected on the basis of the sensitivity to detect clinically meaningful differences, may differ from those standardly used on new active substance. This, too, can result in questions being raised by the EC and later, following marketing approval, the acceptability of the clinical data by prescribing physicians.

Patient recruitment

Patient recruitment is the most challenging aspect of the clinical trial process, consuming approximately 30% of the clinical timeline and often leading to delays.[8] In addition to the usual recruitment demands, biosimilar trials face additional challenges. These include a lack of awareness by investigative sites and patients as to what a biosimilar product is; competition for patients among clinical trials investigating new biological molecules; changes in the standard of care; protocol adherence; and lack of incentives for investigators and patients.

Awareness of biosimilar products

Education of clinical trial site staff, physicians, and patients is critical to the recruitment of subjects into biosimilar trials. An Industry Standard Research report[12] examining ways to improve recruitment into biosimilar studies, addresses a number of recommendations on how to interact and communicate with prospective participants. It also describes potential strategies for enhancing patient recruitment. The report emphasizes the importance of patient education regarding the potential value of biosimilars, including evidence that biosimilars can provide affordable alternatives to more costly, branded therapies, thereby increasing access to treatments that would otherwise be beyond the financial means of many patients.

Competition against new biological molecules

Competition for patient populations is fierce. As of earlier this year, there were 55 Phase III studies listed on clinicaltrials.gov actively recruiting for adult patients with rheumatoid arthritis. Of those, one was investigating biosimilar products. Although not all of the remaining 54 studies are investigating new biological molecules, these numbers help illustrate the level of competition for patients within a single indication.

Protocol adherence

Familiarity with the reference product and/or product treatment and local practices can lead to intersite variation of study procedures and possible protocol deviations. Site support with regard to protocol training and supportive protocol study aids is key to obtaining quality data in biosimilar studies.

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Incentives for investigators and patients

There can be a lack of incentive for investigators regarding participation in clinical trials for biosimilar products, when compared to studies involving new biological molecules. Comparative efficacy and safety studies for biosimilars are often perceived by investigators as having little scientific interest or as lacking novel or interesting study designs. Patients may also not see any advantage to participating in a biosimilar study as they may have access to the reference product as part of their standard of care.

As described earlier, key to overcoming this issue is the education of the site staff, physicians, and patients about the potential value of biosimilars. In some cases, patient recruitment can be accelerated by conducting the studies in countries and markets with the greatest unmet clinical need. Although the quality of research can be very high in these countries, experience in the use of the reference product may be limited. Site support, therefore, remains critical to the success of the clinical study.

Conclusion

Biosimilar development programs face a number of unique operational challenges associated with the guiding principle of establishing similarity between the biosimilar and the reference product. As more and more branded biologics lose patent protection, the race to launch biosimilar products will intensify as manufacturers compete to be among the first to establish their position in a rapidly evolving marketplace. Careful strategic planning and understanding of the operational challenges are crucial to minimize the impact of these issues and to assure the successful development and approval of a biosimilar product.

References

1. IMS Institute for Healthcare Informatics Report. (2011) "The Use of Medicines in the United States: Review of 2010." https://www.imshealth.com/files/web/IMSH%20Institute/Reports/The%20Use%20of%20Medicines%20in%20the%20United%20States%202010/Use_of_Meds_in_the_U.S._Review_of_2010.pdf
2. Brockmeyer C. and Binocrit A.S. (2009) "Assessment of Quality, Safety and Efficacy of Biopharmaceuticals." EJHP *Practice*, 15(2): pp. 38-44.
3. Schneider C.K. (2013) "Biosimilars in Rheumatology: The Wind of Change." *Annals of the Rheumatic Diseases*, 272(3), pp. 315-317.
4. Schiestl M., Stangler T., Torella C., et al. (2011) "Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals." *Nature Biotechnology*, 29, pp. 310–312.
5. European Medicines Agency. (October 2014). Guideline on Similar Biological Medicinal Products. (CHMP/437/04 Rev 1), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
6. European Medicines Agency. (May 2014) Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues (Revision 1). (EMA/CHMP/BWP/247713/2012), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf
7. European Medicines Agency. (January 2010) Guideline on the Investigation of Bioequivalence. (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
8. Food and Drug Administration. (May 2014) draft Guidance for Industry Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf
9. European Medicines Agency. (20 January 2010) Guideline on the Investigation of Bioequivalence. (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
10. International Conference on Harmonisation (ICH) topic E10. (January 2001) Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf
11. Neulasta: EPAR-Scientific Discussion (June 19 2009 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000420/WC500025941.pdf
12. Industry Standard Research (ISR) Report. (2012) Improving Patient Recruitment in Biosimilar Trials, http://www.isrreports.com/product/improving-patient-recruitment-in-biosimilar-trials

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It's Never Too Early for Cold Chain Planning for Cell Therapies

Regulatory scrutiny ups the ante for adoption of logistics management technologies that provide complete chain-of-condition and chain-of-custody tracking.

Tamie Joeckel
Senior Vice President of Client Services and Consulting, Cryoport

Cellular therapies—a category that includes regenerative medicine and immunotherapy—offer the potential to improve the practice of medicine and to fill unmet needs for patients with few or no treatment options. However, your supply chain team may have less experience with these products, which require new technologies, capabilities and resources that may not be available in-house. Moreover, distribution can be challenging, as many of these therapies must be shipped and stored at cryogenic temperatures.

In addition to strict temperature guidelines, these cellular-based therapies have multi-step supply chains that present a new layer of complexity to scheduling and track and trace. Whereas traditional pharmaceuticals have a linear supply chain model that is less time sensitive, many cell therapies have a circular supply chain. For example, the manufacture of an autologous therapy requires obtaining cell materials from a patient, sending the materials to processing and manufacturing facilities, and then shipping the finished product back to the same site for patient administration, leaving no room for error in tracking or traceability.

Biopharmaceuticals are incredibly sensitive to the slightest changes in temperature, pressure, humidity or other conditions. For cell therapies, a very specialized approach that involves both temperature control and scheduling is vital to maintain the integrity of the product. The distribution of cell therapies not only requires constant temperature control but is also extremely time-sensitive. As soon as a sample is taken from a patient, cell loss and degradation begin almost immediately, leaving perhaps only 36-48 hours to get the harvested biomaterials to the manufacturer. Any variation in temperature, or interruption in the supply chain, can impact clinical trial results by compromising data integrity and potentially the product's efficacy and safety.

Many of these programs are global with a centralized manufacturing capacity. Consequently, cold chain transport not only requires a sophisticated understanding of innovative shipping technologies, but continuous monitoring, recording and documentation of the condition of the biologic material throughout the journey—and, if necessary, proactive intervention to remediate issues that arise during shipment. The distribution process also requires reverse-logistics planning, as the packaging must be returned for cleaning, revalidation and recharging.

The complexities surrounding the manufacture and distribution of cell therapies have spawned the development of liquid nitrogen dry vapor shippers and other packaging innovations that enable shipment and storage at stable cryogenic temperatures. They have also sped the adoption of sophisticated logistics systems that provide data collection and active/live monitoring capabilities.

It should come as no surprise that agencies such as the International Society for Biological and Environmental Repositories, the World Health Organization, the FDA, the U.S. Pharmacopeial Convention, the International Air Transport Association and the International Organization for Standardization have issued or are reviewing guidelines for the storage and distribution of biological materials. Such regulatory scrutiny ups the ante for adoption of logistics management technologies that provide complete chain-of-condition and chain-of-custody tracking.

When fully integrated with clinical software, logistics management systems can coordinate smoothly with patient site visits. These systems can also help optimize workflows, ensuring the seamless transit of biological materials from patient to manufacturer and back to the patient. Even if your clinical trial is in the protocol-planning stage, it's not too early to incorporate cold chain logistics into the planning process.

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