Life & Health

Clinical Communiqué

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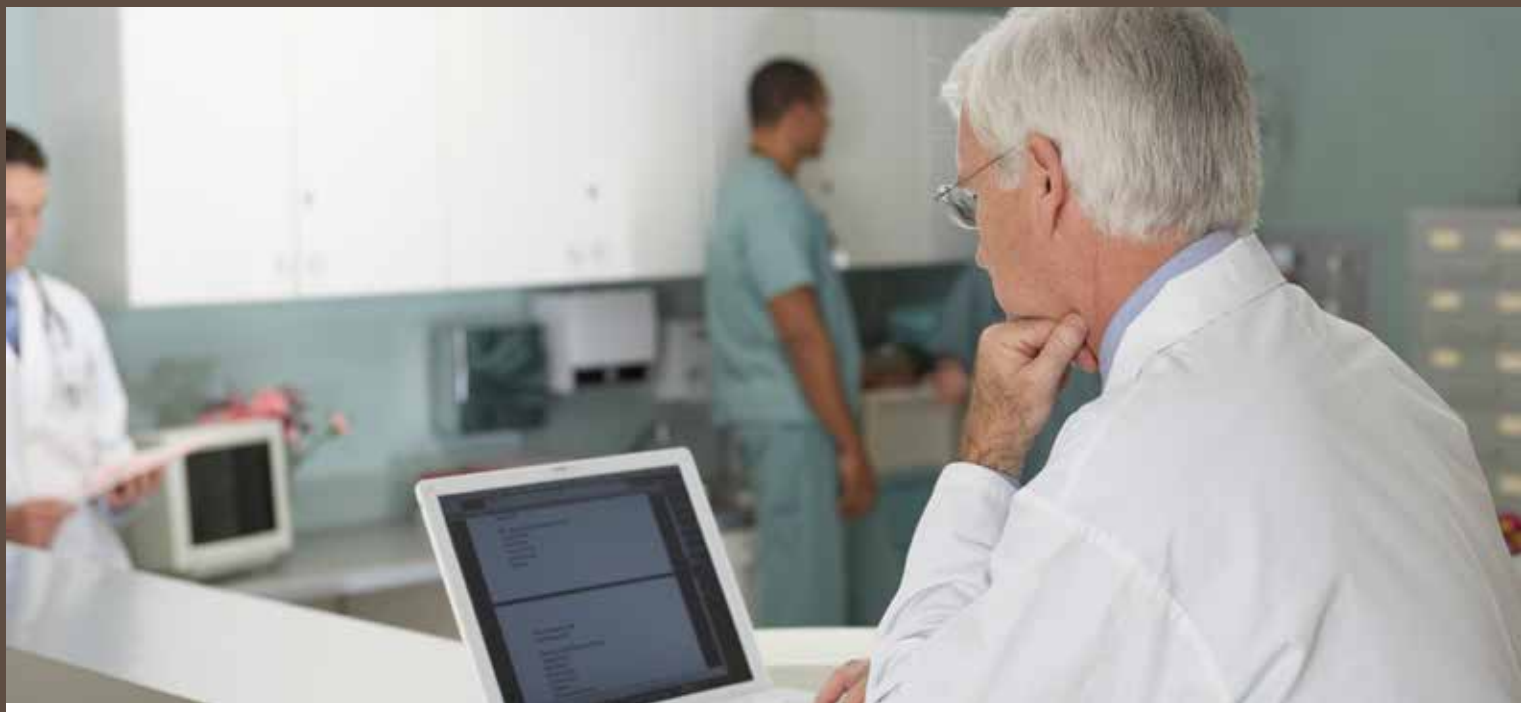

INVESTIGATOR-INITIATED RESEARCH:
Responsibilities and Risks

Increasingly, Pharmaceutical and Medical Device companies are recognizing the value of Investigator-Initiated clinical Research (IIR), also known as Investigator-Initiated Trials (IIT). Recent studies have shown growth rates in the funding by Life Science companies in IITs of as much as 40% – and there is no indication that the trend will slow. In fact, drug and Medical Device companies are demonstrating their support for IITs not just in budgets but also in the formation of in-house programs designed to manage Investigator-Initiated Research.

There are several reasons for the increase in IITs. Even though a drug or device company may commit more than a decade and $1 billion to bringing a new product to regulatory approval and patient use, it is impossible to fully understand all the potential uses and risks of a medical product until it is in the general population. Traditional clinical trials cannot be designed to answer those questions. Questions about additional uses, limits and safety issues may be answered by investigators who initiate carefully focused research.

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INVESTIGATOR-INITIATED RESEARCH:
Responsibilities and Risks *(Continued)*

Both large and small companies find value in IITs. Not surprisingly, large global companies are most likely to maintain their own IIT departments. Pfizer, for example, lists the types of research it considers eligible for support. These candidates reflect similar categories for consideration by other large Pharmaceutical companies and include:

- Clinical studies of approved and unapproved uses involving approved or unapproved Pfizer therapies;
- Observational studies including epidemiology studies and certain outcomes research studies where the primary focus is the scientific understanding of disease;
- Other types of independent research on disease states, including novel diagnostic screening tools and surveys where Pfizer has no direct commercial interest.

In some cases, companies may provide products to the IIT or grants to assist in funding the research. Without proper planning and execution, legal and compliance risks can attach to the company as well as the IIT.

Sponsor and Investigator

In an IIT, the investigator is also the sponsor of the trial, responsible for compliance with all regulatory requirements that apply to both sponsors and investigators. While the investigator's compliance responsibility might seem to insulate the Pharmaceutical or Medical Device company from any legal or regulatory liability, it is important that companies understand their roles in IITs and how to avoid potential, unnecessary risks.

By definition, IITs are unsolicited by the company. Companies may, however, choose to support the study through drug product, grant or administrative assistance. Independent investigators submit preliminary proposals to the company, typically through the company's IIT program or its research division. The proposal will identify the resources sought by the investigator, which can vary from the company's products to study funding or management assistance. The driver for the investigator may be a straightforward interest in advancing medical knowledge or, in the case of a physician investigator, it may be for the benefit of patients or support of a new use for the approved product. For the company, the same drivers may hold true.

The Company's Risks

For the company to move forward, several provisions should be in place:

- A predefined set of criteria for reviewing research requests from independent investigators;
- An established group that will evaluate the proposal. Evaluations should be conducted by medical, R&D and clinical personnel – not marketing people;
- Know what your company's role is in the investigation. Especially important, how will the investigator do documentation, adverse events reporting and compliance requirements?
- The FDA has increased its scrutiny of clinical trials, including in the areas of fraud and abuse. IITs are subject to the same laws as company-initiated compliance in areas such as protection of subjects, informed consent, Sunshine laws, the Anti-Kickback Statute, anti-corruption laws and even the False Claims Act. Scrutiny may be especially keen for trials that receive assistance or any funding from the company. Recognizing this, both AdvaMed and PhRMA have developed guidelines for investigator-initiated trials;
- Have and follow a written agreement that clarifies the company's role in the trial. Questions that should be answered: Who owns the research data, who is responsible for monitoring the trial to ensure the written agreement is followed, who is providing which (if any) specific resources for the trial? The agreement must protect the company in cases such as poor data generation, misleading reporting and violations of anti-corruption laws, both domestic and foreign.

For a growing number of companies, the risks of IITs are far outweighed by the potential benefits, especially in identifying new uses for approved products and additional safety information for discrete patient populations. Despite this positive balance, however, companies must take the necessary steps to ensure that Investigator-Initiated Research is reviewed, approved and conducted in compliance with all regulatory requirements and company policies.

CDRH'S FOCUS ON CLINICAL TRIALS

When the FDA's Center for Devices and Radiological Health (CDRH) released its strategic priorities for 2014 to 2015, clinical trials were prominently featured. In fact, CDRH's Number 1 priority was to strengthen the clinical trial enterprise. The Center identified two goals:

- Improve the efficiency, consistency and predictability of the Investigational Device Exemption (IDE) process to reduce the time and number of cycles needed to reach appropriate IDE full approval for Medical Devices, in general, and for devices of public health importance in particular;
- Increase the number of early feasibility/ first-in-human IDE studies submitted to FDA and conducted in the US.

Backdrop of CDRH's Strategy

CDRH set the stage for its strategic policy in this way: "A key determinant of early US patient access to high-quality, safe and effective devices is whether and when a device developer chooses to study the product in this country, and a key factor in this decision is the time and cost of demonstrating that the developer's product meets our standard for marketing authorization." CDRH notes its commitment to strengthening and streamlining the clinical trial enterprise so that "... medical device clinical trials are conducted in the US in an efficient and cost-effective manner, while maintaining appropriate patient protections." CDRH then explains that it has already taken several actions to expedite the safe initiation of clinical trials in the US including the following:

- Issued guidance and started a pilot program to facilitate the early clinical evaluation of novel device technologies in the US using risk-mitigation strategies that appropriately protect human subjects.
- Implemented process changes to the IDE program, consistent with FDASIA. CDRH's 2013 guidance on FDA Decisions for Investigational Device Exemption Clinical Investigations proposed additional program modifications that allow earlier and more efficient clinical study enrollment.

According to the Center, substantial impacts have already been documented, including the percentage of IDE submissions that received approval decisions authorizing study initiation within two IDE cycles. Those authorizations increased from 46% in FY 2011 to 77% in FY 2013, while the median time to full study approval shrank from 435 days to 174 days.

CDRH'S FOCUS ON CLINICAL TRIALS *(Continued)*

Focusing on New Goals

To achieve its two priority goals, CDRH has identified key targets.

Goal #1: Improve the efficiency, consistency and predictability of the IDE process to reduce the time and number of cycles needed to reach appropriate IDE full approval for Medical Devices in general and for devices of public health importance in particular. Key targets include:

- By September 30, 2014, reduce the number of IDEs requiring more than two cycles to an appropriate full approval decision by 25% compared to 2013 performance and, for disapproved IDEs, to offer all sponsors a teleconference or in-person meeting to occur within 10 days of the IDE decision. By June 30, 2015, CDRH's target is to reduce the number of IDEs requiring more than two cycles by 50% compared to FY 2013 performance.
- By September 30, 2014, reduce the overall median time to appropriate full IDE approval by 25% compared to FY 2013 performance and, by June 30, 2015, reduce the overall median time to full appropriate IDE approval to 30 days.

Goal #2: Increase the number of early feasibility/first-in-human IDE studies submitted to FDA and conducted in the US.

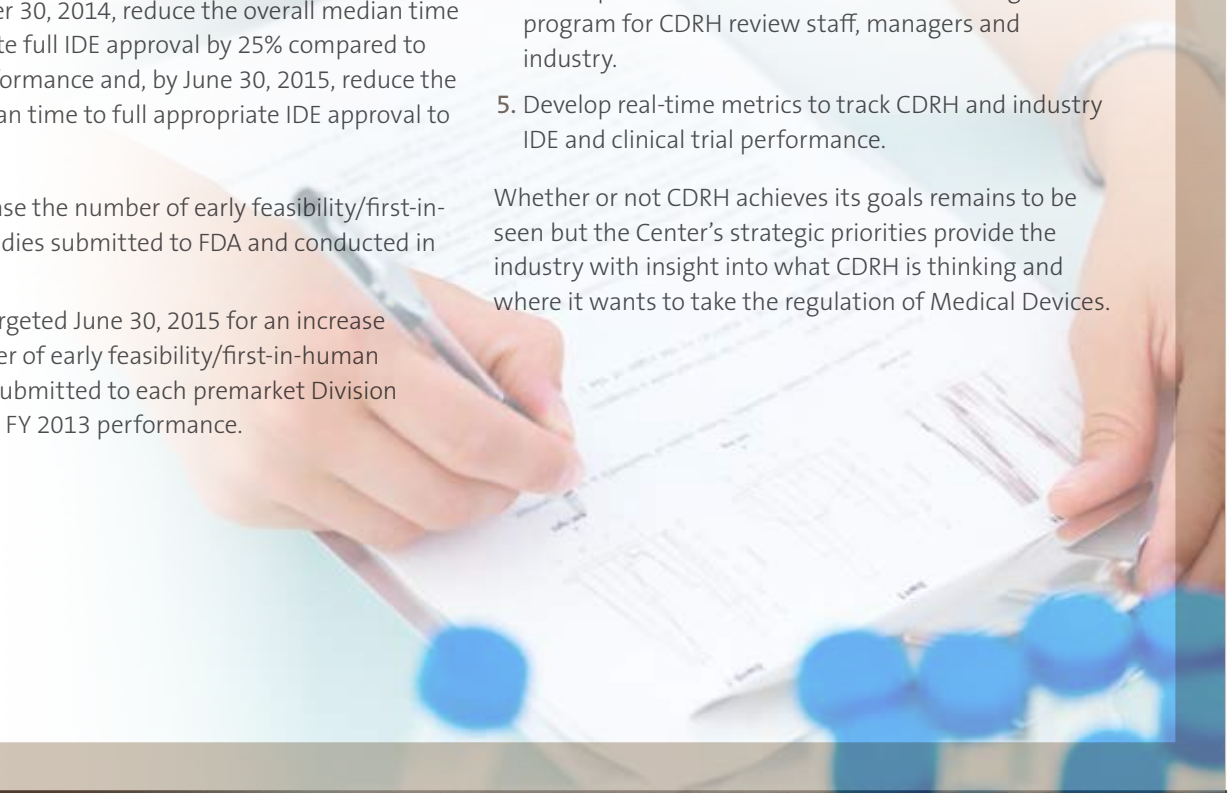
- CDRH has targeted June 30, 2015 for an increase in the number of early feasibility/first-in-human IDE studies submitted to each premarket Division compared to FY 2013 performance.

Achieving Its Goals

With a clear view of its goals and targets, CDRH has developed specific steps to take in order to achieve those goals and targets. Those steps include the following:

1. Establish a premarket clinical trials program in the Office of Device Evaluation. This program will be responsible for the oversight and performance of the IDE program and development and implementation of policies that contribute to the initiation and successful execution of Medical Device clinical trials.
2. Formalize the incorporation of its benefit-risk framework, including patient-specific factors such as tolerance for risk and perspective on benefit, into the IDE process.
3. Establish a process to efficiently and objectively resolve application-specific IDE issues to reduce the number of multi-cycle IDEs.
4. Develop a clinical trials education and training program for CDRH review staff, managers and industry.
5. Develop real-time metrics to track CDRH and industry IDE and clinical trial performance.

Whether or not CDRH achieves its goals remains to be seen but the Center's strategic priorities provide the industry with insight into what CDRH is thinking and where it wants to take the regulation of Medical Devices.



PRINCIPALS OF CLINICAL TRIAL TRAINING:

Teaching Clinical Professionals as Adults

A regulatory requirement across all of clinical research is that Investigators and others must have training and experience that qualifies them to engage in human clinical research. A key and growing challenge is ensuring that research personnel not only receive the right training for their roles but that the training itself is effective.

Jeffrey Cooper, MD, of the WIRB-Copernicus Group and Carrie McKeague, PhD, of UL EduNeering recently sat down and discussed how, in order for training to be effective, it must deliver relevant and appropriate content in an educational design that fits the learning style and needs of the intended audience.

According to Dr. Cooper, training is an essential component of Institutional Review Board (IRB) "qualification" to ensure patient safety. Within the IRB are several layers of functional roles, each with its own set of regulatory training requirements. Because there is limited overlap in these training requirements, "qualification managers" must develop role-based curricula that meet the needs of each role.

Investigator – Obligations Consent	IRB Staff – Operations
• Get IRB approval • Follow the protocol • Submit modifications • Ensure staff are qualified • Supervise the research • Protect the subjects • Submit continuing review • Obtain consent • Document consent • Retain research records	• Aware of regulatory requirements and acceptable standards • Familiar with the purpose of the research • Understanding their assigned tasks • Competent to perform delegated tasks • Informed of any changes to the research

Role-based training is now widely adopted in clinical research training. However, there is broad disparity in the perceived effectiveness of these trainings. Dr. McKeague suggests that training design is a key factor in determining ongoing training effectiveness. To make this personally relevant, she suggests considering the characteristics of the best training you have taken as an adult. It is likely this training included clear objectives, addressed "why" it was important to you, contextualized the topic and allowed you opportunities to solve problems using your new knowledge and skills.

PRINCIPALS OF CLINICAL TRIAL TRAINING:

Teaching Clinical Professionals as Adults *(Continued)*

Malcolm Knowles, a recognized expert in the field of adult education, identified several traits adult learners have that are essential to good training design. These include:

- Goal-Oriented
- Relevancy-Oriented
- Practical
- Have a foundation of life experience and knowledge
- Are autonomous and self-directed
- Need to be shown respect

Another strategy for developing effective adult learning is utilizing both a Subject Matter Expert and an Instructional Designer. Together, these developers bring together two individual skill sets to create great training. Citing a study by Neil Charness* that defined differences between chess experts and masters, Dr. McKeague describes how, while novices tend to see next steps in a given problem, Subject Matter Experts can see patterns and sequences. They have expert knowledge in a domain area, have automated their knowledge processing and have often forgotten critical links and paths that helped them make those associations. However, they have limited or no knowledge of instructional strategies to engage learners.

*Charness, N. (1989). Expertise in chess and bridge. In D. Klahr and K. Kotovsky, eds., Complex information processing: The Impact of Herbert A. Simon, pp. 183–208. Hillsdale, N.J.: Erlbaum.

For example, a less experienced Quality Risk Management practitioner may implement ICH Q9 guidance into his or her company's SOPs, but struggle with incorporating nuances of the recent TransCelerate Risk-Based Monitoring White Paper that could have positive implications to quality, compliance and cost.* A QRM expert may intuitively know this and direct less experienced people accordingly, but be unable to help them learn "why" these directions add value.

* http://www.transceleratebiopharmainc.com/our-initiatives/risk-based-monitoring/

Instructional Designers, on the other hand, make instruction relevant by understanding the audience, engaging by incorporating instructional strategies and effective by allowing for interaction and practice.

Instructional Designers strive first to understand the audience for the training. They work with Subject Matter Experts to identify what the audience needs to learn. They develop objectives and ensure that content matches those objectives, and revise and rewrite content to shape them. Importantly, they structure content and activities to allow for learner application and practice. Finally, they develop assessments as a feedback mechanism for both learners and managers.

Working together, Subject Matter Experts and Instructional Designers identify learning objectives: what type of knowledge
are you teaching, and what do you want the learners to walk away with? Then, useful tools such as Bloom's Taxonomy of Instructional Strategies* can be applied to design the learning program. This model informs adult learning strategy through two "Dimensions." The first is a "Knowledge Dimension," which defines the kinds of information to be learned. These include, in increasing complexity, facts, concepts, procedures and cognitive awareness. There is also a "Cognitive Process Dimension," which describes what the learner is intended to do with this new knowledge. These dimensions are recall, understanding, application, analysis, evaluation and creation. At the intersection of these dimensions is an appropriate instructional strategy for adult learning.

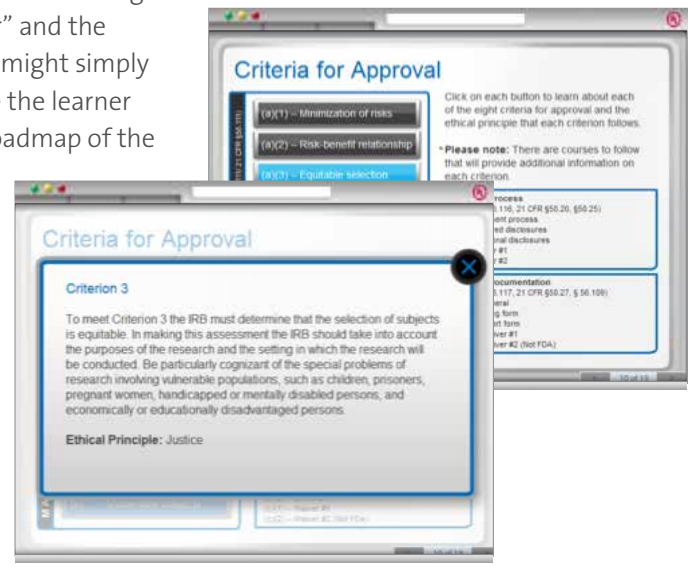
* http://www.celt.iastate.edu/teaching/RevisedBlooms1.html

A specific application for IRB ethics training might be for this objective: "After completing this course, you will be able to recognize the eight criteria for IRB approval and

PRINCIPALS OF CLINICAL TRIAL TRAINING:

Teaching Clinical Professionals as Adults *(Continued)*

the ethical principal that each criterion follows." In this example, the Knowledge Dimension is "Conceptual," the Cognitive Dimension is "Remember" and the intersecting instructional strategy is "Recognize." While an expert might simply list the eight criteria, the Instructional Designer will seek to engage the learner in the learning process. In this example, the learner sees a visual roadmap of the criteria with instruction to click and open each criterion in its own, focused description and matching ethical principle. A quiz or content-related activity is often included to verify training effectiveness.



Qualification training for clinical researchers is a regulatory requirement. Given both time and resource constraints, and the high level of turnover, it is essential that this training be effective. Two keys to consider when developing effective training are to pair a Subject Matter Expert with an Instructional Designer and to account for the characteristics of Adult Learners.

About UL EduNeering

UL EduNeering is a business line within UL Life & Health's Business Unit. UL is a global independent safety science company offering expertise across five key strategic businesses: Life & Health, Product Safety, Environment, Verification Services and Enterprise Services.

UL EduNeering develops technology-driven solutions to help organizations mitigate risks, improve business performance and establish qualification and training programs through a proprietary, cloud-based platform, ComplianceWire®.

For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university. Additionally, UL maintains exclusive partnerships with leading regulatory and industry trade organizations, including AdvaMed, the Drug Information Association, the Personal Care Products Council and the Duke Clinical Research Institute.