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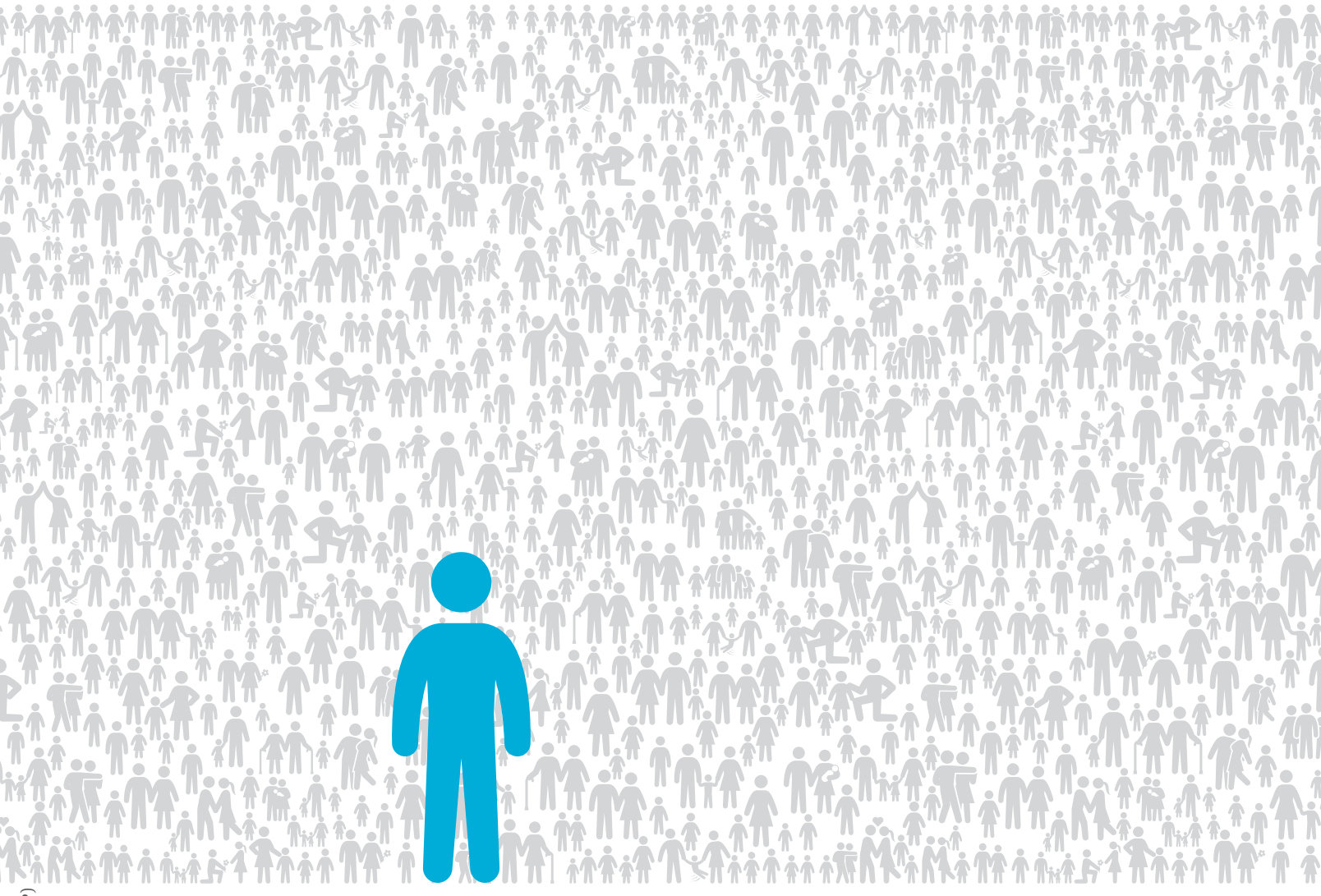

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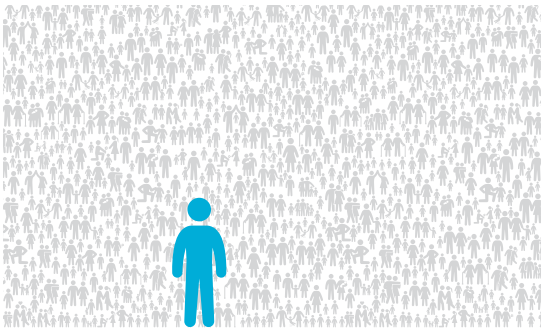

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GUEST EDITOR'S MESSAGE

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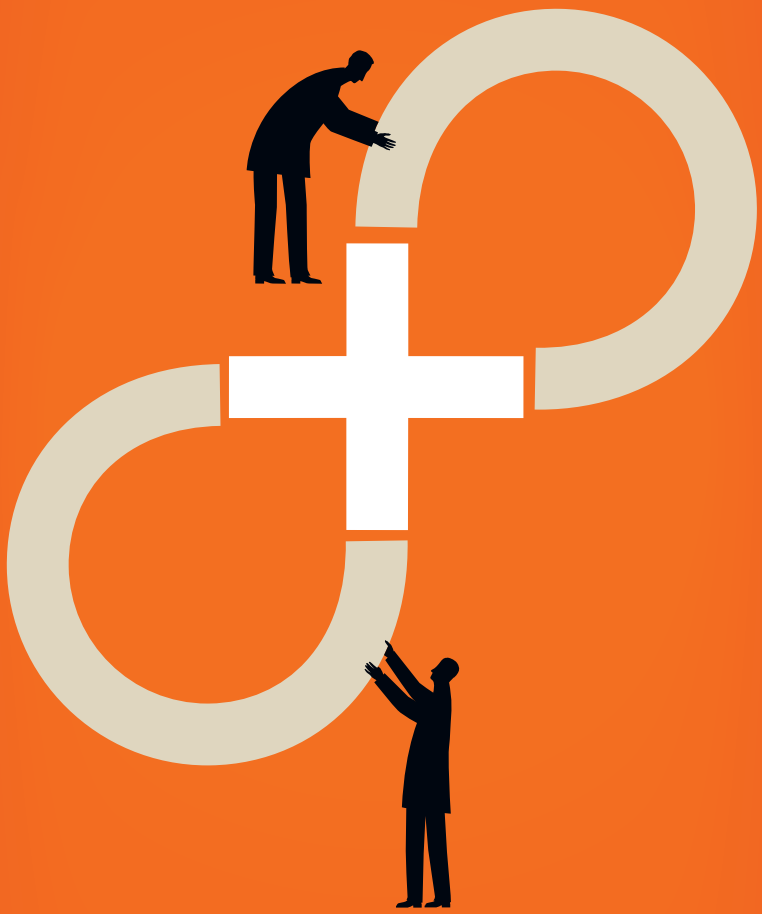
[DOI: 10-14524/CR-15-4083]

To Infinity – *And Beyond*



From the vantage point of my small corner of the world, the field of clinical research has always dazzled me with its vistas of endless possibility, creativity, and constant re-invention. In this issue of *Clinical Researcher,* we have collected a mix of articles from authors involved in a myriad of clinical studies and clinical study activities that could be considered "outside the box," to explore how diverse and exciting clinical research is now and will continue to be.

When many of us enter (or fall into) our first job in clinical research, we learn about and participate in the execution of the classic drug development model—Phase I before Phase II before Phase III, licensure, and into Phase IV. However, this is just the tip of the iceberg we find as we delve deeper into this fascinating field where we build our careers and, sometimes, even realize our dreams.

It is the ultimate goal of clinical research to discover new treatments, and to improve and even save patients' lives, and the paths that lead us there are becoming increasingly complex. This complexity is driven in line with the fast-paced growth of technology (both information-based and science-based), an increasingly stringent regulatory framework worldwide, and a call from patients themselves for a more patient-focused approach to healthcare, including clinical research.

A Paradigm Shift?

In our cover story, Helen Harris describes how the one disease/one drug paradigm is being challenged in the clinical trial arena. She defines personalized medicine as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease," and proceeds to describe how diagnostic biomarkers can be used to personalize treatment of study subjects or inform inclusion/exclusion criteria in clinical trials.

Moreover, this article describes how such an approach may eventually be used for limiting sample sizes required for pivotal clinical trials, shortening enrollment timelines, and ultimately making the regulatory pathway to licensure more efficient.

Patient Sensitivity

Clinical researchers must always be sensitive to subjects with special needs; Sandra Mutolo presents the successful strategies employed in meeting the needs of geriatric subjects participating in an Alzheimer's study.

With the aging population, more research is essential to ensure that treatments are effective for older adults, but researchers must be able to address certain special needs associated with this population: fatigue, sensory deficits, mobility

To read our Article Submission Guidelines, see page 71.

issues, and the involvement of caregivers as co-participants. There is a wide range of abilities within the aging population, and flexibility is key in addressing the needs of individual subjects as study interactions progress.

DIY Research?

More and more physicians are becoming interested in conducting their own clinical research—not just as principal investigators, but as sponsors in their own right; but how can this be done? Sharma et al. have created a primer for the interested physician on how to implement and execute investigator-initiated clinical trials. In this article, the authors have presented the many issues involved in assuming the role of both sponsor and investigator, from interacting directly with regulatory agencies, to investigational product management and logistics, to ensuring independent monitoring of the study.

Technologically Savvy Clinical Research

It is exciting to see how our increasing ability to access information is fueling the clinical research enterprise. Jonathan Calderwood describes how rethinking the global supply chain for biologics, by leveraging complex technological tools that allow iterative forecasting in conjunction with innovative kit design and strategic labeling operations, can efficiently supply clinical trials in far-flung corners of the world with a very limited supply of investigational product. Case studies are presented to show the success of this approach in both time and cost savings.

In the medical device arena, Ribbens and Frestedt are using innovative approaches to mine data in available databases to optimize postmarketing surveillance reports. It is a challenge for medical device companies to provide reports to regulatory bodies based solely on the information reported to them from product users. Information can reside in a variety of databases maintained by governments and other agencies. In this article, the authors describe how, by asking the right questions of these databases, information can be compiled into a robust data package for postmarketing surveillance reports to regulatory bodies.

In another medical device article, Matthew Harris and a colleague provide a primer for compiling comprehensive clinical evaluations reports for devices in compliance with European directives for submission within the European Union.

Onward and into the future, Hermioni Zouridis describes what can be done to bring big data into controllable, usable, interpretable format. In this article, the author explores how aggregated information known as "big data" can be analyzed using enhanced data-mining techniques—biovisualization to "see" patterns and to pull out useful information. In clinical research, biovisualization can lead to increased efficiencies in data analysis and ultimately add a burst of speed on the road to licensure.

Where to Now?

The clinical research field is growing by leaps and bounds. As our authors have shared through their experiences, it is apparent that creative thinking in conjunction with ever-evolving technologies continues to enable us to surmount challenges in the drug development process, even under the spotlight of more stringent regulatory requirements. However, as we in the industry continue in our daily activities as coordinators, monitors, data managers, or whatever our current role may be, we must be asking, "What will happen next?"

In a recent survey of professionals conducted by ACRP and CenterWatch (described in these pages by Terri Hinkley in her message as the interim executive director of ACRP), the majority of respondents expected their duties and responsibilities to increase in complexity. While this may seem to be daunting, there is another message sounding loud and clear from one of the other authors contributing to this issue. According to Kevin Duffy, the biopharmaceutical sector of our industry is taking a serious approach to proactively planning recruitment strategies to meet its need for talented people by investing in activities that maximize employee satisfaction and retention. This is good news for the members of a highly skilled and creative workforce to take with them as they climb that next mountain.

The classic drug development model is just the tip of the iceberg we find as we delve deeper into this fascinating field where we build our careers and, sometimes, even realize our dreams.

DISCLAIMER

The opinions expressed in this article are strictly the viewpoint of the individual author, and do not represent the opinions of her company.

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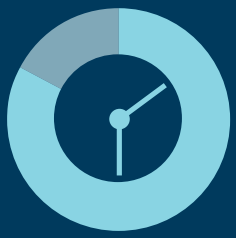
BY THE NUMBERS

Offering glimpses of how some researchers and study teams are thinking (or being prompted to think) outside the box when it comes to evolutions in clinical trial design and conduct.

As an alternative to a 50/50% chance of randomization to treatment or placebo, researchers have proposed a new **"two-by-two blind trial"** design, in which participants are placed in a group with either a high probability **(70%)** or low probability **(30%)** of receiving treatment.

Source: Princeton University, www.eurekalert.org/pub_releases/2015-06/puww-gct061015.php



In the first fully double-blinded jet lag study with a bright light therapy device, **83%** of the 25-member treatment group was free of typical jet lag symptoms in the post-flight measurement period, compared to **55%** of the 30-member control group.

Source: Valkee, www.prnewswire.com/news-releases/humancharger-headset-reduces-jet-lag-symptoms-in-worlds-first-placebo-controlled-clinical-field-trial-with-any-bright-light-device-506745261.html

When asked to imagine that they were taking part in genome sequencing research with the option to receive personal results, **98%** of nearly 7,000 participants from 75 countries wanted to know about genes linked to treatable conditions that were serious or life-threatening—even if the chance of such conditions occurring was as low as 1%.

Source: European Society of Human Genetics, www.eurekalert.org/pub_releases/2015-06/esoh-pwa060415.php

INTERIM EXECUTIVE DIRECTOR'S MESSAGE

Terri Hinkley, RN, BScN, MBA, CCRC

[DOI: 10.14524/CR-15-4081]

Reading Between the Lines of Career and Salary Trends

I've just spent some time reading through the results of a survey—*2015 Career and Salary Benchmark Reports*—conducted jointly by ACRP and CenterWatch, through which we received feedback from more than 2,500 clinical research professionals. I thought I'd share some of my observations, some affirming what I already believed and a few that surprised me.

First, let's look at a finding that didn't surprise me at all. While the U.S. economy has been improving in fits and starts since the recession of 2008, recovery has been relatively slow. However, our survey revealed nearly 90% of respondents feel secure about their status, with about half reporting they feel "very secure." (Note: More than 90% of our respondents came from the United States.)

I think those numbers speak to the fact that there remains a shortage of qualified job applicants. "The demand for talent has certainly outpaced the growth in supply of people coming into the industry," Tom McGoldrick, PAREXEL's vice president of talent acquisition, recently told *The CenterWatch Monthly.*

It's no secret that sponsors, contract research organizations (CROs), principal investigators, and site directors must put more energy into holding on to their star performers.

Workforce development is a problem in our industry that will take dedicated attention to fix, and it won't be easy or fast.

Doing More With Less

Along with job security come greater expectations from management. Job responsibilities for existing professionals continue to increase. Some 40% of clinical research coordinators (CRCs) expect to take on additional tasks in the coming years, and among all survey respondents, 61% said increased workload was their top career challenge. Across the board, about 40% expect workload to increase significantly. The work is going to get harder, too: 59% expect their duties and responsibilities to increase in complexity.

We have been hearing, and I know from firsthand experience, that studies are becoming increasingly complex. Due to rising costs, increased competition, and increased technological ability, there is greater pressure to get as much data as possible from every study.

Roles are evolving, CRCs are taking on more responsibilities historically held by monitors/clinical research associates (CRAs), and CRAs are taking on more responsibilities related to data monitoring and evaluation with the advent of risk-based monitoring. (I spoke on this topic at a Drug Information Association conference in June. In an upcoming column, I'll report back on what I heard from attendees.)

Onward and Upward?

Upward mobility—or lack of—remains an issue, too.

Among sponsors and CROs, our survey found that only one-third believed the best route to promotion and raises came from within their own organization. When our full survey population is included, that figure actually drops to 28%. Nearly half believe they'll need to find a new job with a new employer to move up. They're probably right.

The vast majority of organizational charts are shaped like upside down funnels. There are simply fewer management positions closer to the top. As employees move up the ladder, there is more competition for fewer slots.

It's a bit of a paradox for many ACRP members: The better your organization's leadership, the less your chances of upward movement there, forcing you to leave your organization for a more senior position. This turnover, coupled with the

shortage of experienced staff to take the place of the departed, causes significant staffing issues in many organizations. (Note: In our December 2015 issue, we'll take a closer look at career strategies in today's clinical research environment.)

Surprise, Surprise

Now, let's take a look at one finding that surprised me only by how loud and clear the message was: certification pays—in more ways than one. Our survey found that the median salary for CRCs was 11% higher for those with certification, while certified CRAs and certified registered nurses earned 6% more than noncertified colleagues. I'd argue those figures should be even higher, but they're definitely going in the right direction.

Management sees the benefits of certification, too. Companies paid for the ACRP certifications held by 90% of qualified CRO staff.

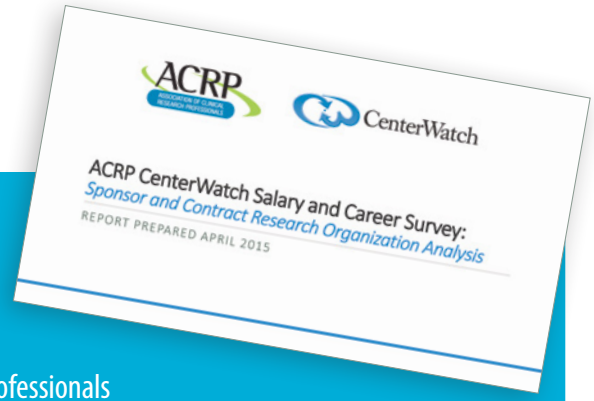
Survey results also show that employers value professional association membership. Companies paid for memberships in our association held by 95% of CRO staff, by 92% of pharmaceutical/biotech staff, and by 99% of medical device staff.

I was also happy to see that employers support education and training, though I hope those numbers continue to climb. Among those mentioning it in the survey, 57% said their companies allow them to take advantage of education opportunities, 49% of the companies pay for certification exams, 48% pay for meeting/training/development attendance, and 45% have an in-house training/development department.

The Power of Data

Our industry needs objective, high-quality data; otherwise, it is impossible to make informed decisions about important matters such as career, job performance, and salary expectations. Partnering with CenterWatch, we feel we've gathered data of significant worth to both individual members of the clinical research team and to the clinical research enterprise at large. Watch this space. We'll continue to work with trusted partners to produce the kind of data you need. If you have thoughts about what you'd like to see, please e-mail me at thinkley@acrpnet.org.

Terri Hinkley, RN, BScN, MBA, CCRC, (thinkley@acrpnet.org) is the interim executive director of the Association of Clinical Research Professionals (ACRP), based in Alexandria, Va.



Learn more about how employment practices are viewed by clinical research professionals with the ACRP CenterWatch Salary and Career Survey. Visit **acrpnet.org/2015salary** for more info.

TABLE 1: Certifications Paid for by Company

Please select which of the following certification(s) and/or membership(s) your company will pay for.	CRO (% mentioning paid for by company)	Pharma/Biotech (% mentioning paid for by company)	Medical Device (% mentioning paid for by company)
Association of Clinical Research Professionals (ACRP)	98%	94%	96%
Society of Clinical Research Associates (SoCRA)	50%	58%	68%
Drug Information Association (DIA)	13%	39%	7%
Regulatory Affairs Professionals Society (RAPS)	13%	36%	45%

TABLE 2: Memberships Paid for by Company

Please select which of the following certification(s) and/or membership(s) your company will pay for.	CRO (% mentioning paid for by company)	Pharma/Biotech (% mentioning paid for by company)	Medical Device (% mentioning paid for by company)
Association of Clinical Research Professionals (ACRP)	95%	92%	99%
Society of Clinical Research Associates (SoCRA)	49%	65%	67%
Drug Information Association (DIA)	27%	57%	9%
Regulatory Affairs Professionals Society (RAPS)	14%	38%	45%

Source: ACRP CenterWatch Salary and Career Survey: Sponsor and Contract Research Organization Analysis. APRIL 2015

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80% The pass rate for the Home Study Test is now 80% to be in alignment with ACRP professional development standards.

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HOME STUDY
Research "Outside the Box"

Clinical Evaluation Reports for Medical Devices

PEER REVIEWED | Matthew J. Harris, BA | Joy L. Frestedt, PhD, RAC, CPI, FRAPS
[DOI: 10.14524/CR-15-0002]

A clinical evaluation report (CER) is an "assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device."[1] Most medical devices marketed outside the United States (U.S.) need a CER to assess and analyze the clinical data, and to document device safety and performance throughout the product life cycle.

LEARNING OBJECTIVE
After reading this article, the learner should be able to write a basic clinical evaluation report (CER) for a class 1 medical device using the basic format provided.

DISCLOSURES
Matthew J. Harris, BA, and Joy L. Frestedt, PhD, CPI, RAC, FRAPS:
Nothing to disclose

The pathway to market for a medical device must comply with the regulations of the country where the product is marketed. In the European Union (EU), several steps are required. Every medical device must be supported by a technical file or design dossier including the CER and other critical components, such as product specifications; intended uses; manufacturing processes; shelf life, sterility, and other test reports; Essential Requirements checklists; vigilance and medical device reporting procedures; references to standards and guidelines; and more.

The U.S. does not require a CER for a medical device; however, the U.S. Food and Drug Administration (FDA) regulations require a thorough "Report of Priors"[2] with data similar to the data reviewed in the CER (see Figure 1).

CERs assess and evaluate all clinical data available for a medical device to verify the safety and performance of the device with a careful analysis of the risks and benefits. According to the EU's Council Directive 93/42/EEC[3] and Medical Device Directive (MedDev) 2.7.1,[1] every CER must follow a documented, defined, and methodologically sound procedure.

Initial Conformity Assessment

Typically, the CER is started as the medical device is being designed, developed, and initially manufactured for the market. The CER is included in the technical file or design dossier, so the notified body can verify the clinical data about the device conform to the essential requirements. This process early in device development is called the initial conformity assessment.

Regardless of when the CER is first developed, it must evaluate all the clinical data available for the device to determine if the device is safe and performs as indicated under normal conditions of use. The CER must also draw conclusions about whether the known and foreseeable individual and overall risks and adverse events are acceptable when weighed against the benefits expected from the normal functions of the device.

Annual CER Updates?

Although no requirement states exactly how often to update the CER, an update is required whenever new data about device performance, risks, benefits, or safety become available. Any changes to risk mitigation activities, instructions for use, or product literature related to safety or performance should signal a need to update the CER.

The CER should also be reviewed well before any planned notified body audits to ensure the clinical evidence continues to support the safety and performance of the device. This CER review should determine if an updated CER is needed to meet the Essential Requirements. Decisions about updating the CER should be documented in the technical file or design dossier, with a signature and date indicating the person who made this decision.

Evaluator Selection and Signature

In the EU, MedDev 2.7.1[1] suggests the evaluator must know the device and how it is used, and the

FIGURE 1: U.S. and EU Regulatory Pathways to Medical Device Approval

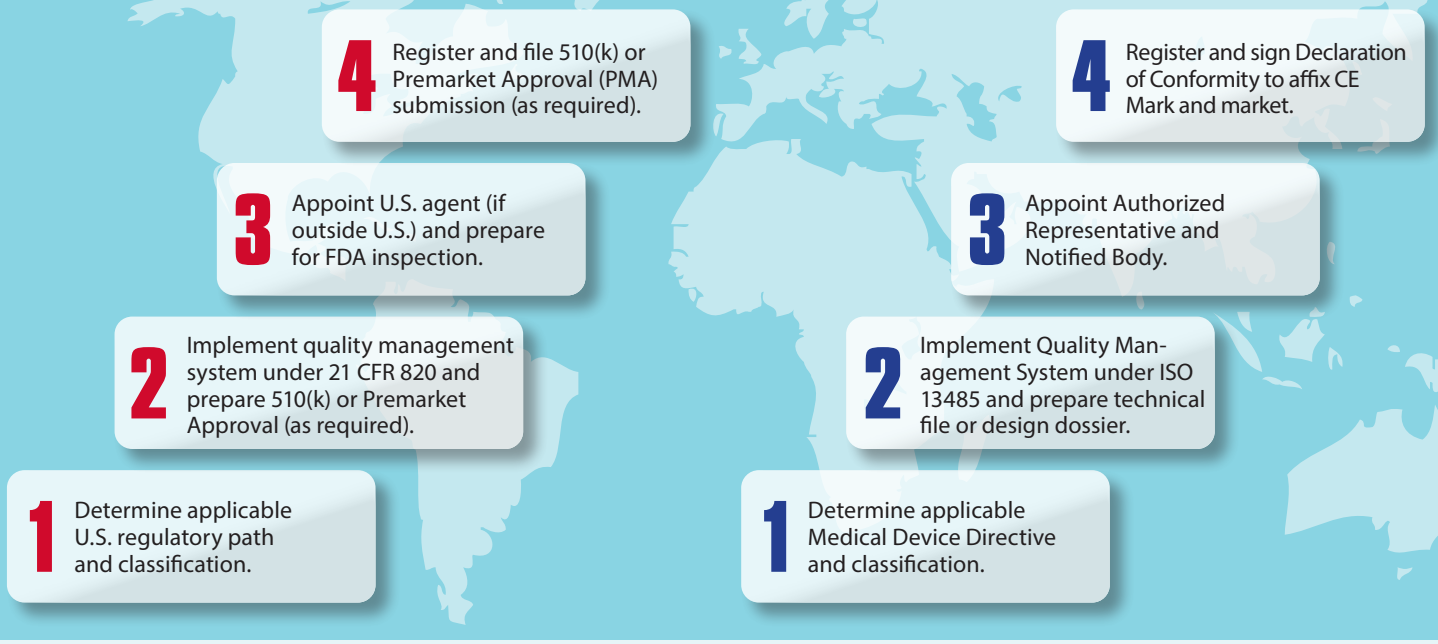

Figure 1 provides an overview of several steps to follow when placing a device on the market in the U.S. or the EU and the steps are further explained below.

U.S. REGULATORY PATHWAY

For **STEP 1**, determine if the device is class 1 (General Controls), 2 (General and Special Controls), or 3 (General Controls and Premarket Approval).

For **STEP 2**, determine appropriate predicate device (if class 1 or 2 following a Premarket Notification or 510(k) path) or if class 3, prepare for Premarket Approval (PMA); manufacturing and testing must comply with FDA 21 CFR 820 QSR (Quality System Regulation) in the *Code of Federal Regulations*.

For **STEP 3**, the authorized agent must be in the U.S. and qualified to handle regulatory requirements.

For **STEP 4**, the sponsor must register and pay applicable fees per the Medical Device User Fee and Modernization Act prior to submission of 510(k) or PMA.

Most medical devices marketed outside the United States need a CER to assess and analyze the clinical data, and to document device safety and performance throughout the product life cycle.

EU REGULATORY PATHWAY

For **STEP 1**, choose 93/42/EEC: Medical Device Directive;[3] 90/385/EEC Active Implantable Medical Device Directive;[4] or 98/79/EC *In Vitro* Devices Directive[5] AND determine if class 1 (sterile or non-sterile), II (a or b), or III (highest risk; List A or B for *in vitro* devices).

For **STEP 2**, choose an international standard for quality management system compliance; establish technical file for lower risk devices or design dossier for higher risk devices (with more complicated files).

For **STEP 3**, choose an "Authorized Representative" in the EU qualified to handle the regulatory requirements, and a "Notified Body" accredited and authorized by EU regulatory authorities to audit medical devices.

For **STEP 4**, register any class 1 devices with the Competent Authority where the Authorized Representative is based and note most Member States do not require registration of class IIa, IIb, or III devices. Sign the Declaration of Conformity, a legally binding document where the manufacturer states the device complies with all EU requirements for CE Marking.

For example, in the EU, the Essential Requirements, defined in Annex 1 of Council Directive 93/42/EEC[3] as amended in 2007/42/EEC[6] (effective 21 March 2010), require a clinical evaluation for all medical devices:

> Annex I, 6a. Demonstration of conformity with the essential requirements must include a clinical evaluation under Annex X.
>
> …AND…
>
> Annex X, 1.1. ...confirmation of conformity with the requirements concerning the characteristics and performances ... under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio ..., must be based on clinical data. The evaluation of this data, hereinafter referred to as 'clinical evaluation'... must follow a defined and methodologically sound procedure…[3]

evaluator must have sufficient research methodology expertise to read the medical literature and understand the "clinical investigation design and biostatistics," as well as the "diagnosis and management of the conditions" where the device is used. The CER "should be signed and dated by the evaluator(s) and accompanied by the manufacturer's justification of the choice of evaluator."[1]

The regulations do not state explicitly who is competent to write or review a CER, although scientific/medical prowess, clinical training, and experience writing a CER are required. Also required is a rigorous and impartial assessment of the clinical data.

The manufacturer is supposed to choose an independent and unbiased evaluator with appropriate qualifications (e.g., an advanced degree), experience, and understanding of the device and the relevant disease state and the medical literature. The evaluator/author is responsible to search for and identify all of the relevant clinical data, to select the appropriate clinical data, and to analyze and draw conclusions from the clinical data regarding the clinical safety and performance of the device.

A good practice while writing the CER is to address the question: "Do the clinical data clearly document the benefits of using this specific device outweigh the risks to the patient?"

CER Formats and Inputs

The CER guideline in MedDev 2.7.1[1] provides a Clinical Evaluation Checklist for Notified Bodies to evaluate the CER and the following CER standard format:

- General Information
- Device Description and Intended Use
- Indications and Claims
- Evaluation Context and Clinical Data Types Chosen
- Summary and Appraisal of the Clinical Data
- Data Analysis
  - » Performance
  - » Safety
  - » Product Literature and Instructions for Use
- Conclusions

Good CER practices include sections about the risk/benefit analysis for the device, equivalent devices, and three separate data analysis sections for each of the data sources (one each for clinical investigations, clinical literature, and clinical experiences) (see Table 1).

The U.S. FDA corollary of the CER (i.e., the "Report of Priors" in 21 CFR 812.27) requires a bibliography of all publications related to the safety or effectiveness of the device, a summary of all other unpublished information obtained by the sponsor, and data from nonclinical laboratory studies.[2]

TABLE 1: Common CER Inputs

CER section	Description of data types	Types of data to consider
Clinical Investigations	Data collected by the manufacturer through pre- and postmarket human clinical trials of the device.	First-in-human, Investigator Device Exemption, Humanitarian Device Exemption, postmarket surveillance, postmarket clinical follow-up, registries, and investigator-initiated trials
Clinical Literature	Data from published and unpublished reports about using the device (as well as equivalent devices) in human studies.	Peer-reviewed, randomized, and controlled trial reports; meta-analyses; systematic reviews; comparative studies; cohort studies
Clinical Experiences	Data from individual human uses of the device (as well as equivalent devices) outside a clinical trial or study report.	Complaints and user reports collected by sponsor; failure modes and effects analyses; medical device reports; Manufacturer and User Facility Device Experience (MAUDE) database reports; FDA Warning Letters, recalls, and total product life cycle reports

Device Family Members and Equivalent Devices

One difficult decision when writing a CER is to determine the scope of the CER and exactly which devices will be included in the CER. A manufacturer may include in one CER all "equivalent" devices (e.g., all similar orthopedic surgical instruments with the same intended use and the same clinical, biological, and technical characteristics).

- **Clinical equivalence** pertains to the indications for use, patient populations being treated (age, gender), expected clinical effects, and the site of application in the body.
- **Biological equivalence** relates to the cellular and biological responses arising from the device materials contacting body cells, fluids, and tissues.
- **Technical equivalence** includes the specific and detailed design features, physiochemical properties, and principles of operation.

Defining the boundaries of the equivalent devices and/or device family member is important for the CER and a careful gap analysis comparing

each equivalent device to the device being evaluated should be performed and documented in the CER. Devices with different clinical, biological, or technical characteristics and which have different safety or performance profiles are not equivalent, and typically require separate CERs.

Clinical Investigations

The results from clinical trials evaluating the safety and performance of the device in the intended population will be the most important data to consider in the CER. In general, two randomized, placebo-controlled clinical trials with sufficient statistical power to show a difference between the test and control groups are considered the "gold standard" for clinical evidence. However, this level of clinical evidence is often not available, and the evaluator is forced to consider multiple smaller and less well-controlled trials or case series.

A good practice when considering multiple clinical trials with the study device is to rank the quality of the study design and to assign larger, more rigorous studies in the analysis with more weight than smaller, less rigorous studies.

For high-risk devices, the manufacturer is typically required to run a clinical trial to document the safety and performance of the device, and to assess the benefits and risks to the patient when using the device. The clinical trial design type is not restricted, and may involve a parallel group, crossover, or other trial design; however, trial designs with comparator groups and randomized trial designs are more rigorous than simple observational studies, regardless of the study groups.

In addition, the size of the trial is important, since case studies and small case series have less statistical power, and are usually less rigorous than a single, large, randomized, placebo-controlled clinical trial.

Clinical Literature

Literature searches about the disease state or the surgical procedure are not the purpose of the CER; staying focused on the safety and performance of the device is the purpose, and a fair and well-balanced presentation of the data analysis is required. Clinical literature can be found in many places, including (but not limited to) internal libraries, anecdotal documents provided by subject experts, and literature searches of publicly available and fee-for-service literature databases.

The literature-searching protocol should be robust, reproducible and rigorous, and should specify the databases, search terms, and selection criteria used, with justifications for each item (i.e., no "cherry picking" is allowed). Each piece of literature should be assessed for suitability (relevance) and contribution of study results to understanding the safety and performance of the device (quality).

A good practice is to rank and describe the strongest data first (e.g., a meta-analyses of several independent studies using the device should be more highly ranked than individual case reports of clinical investigations using equivalent devices). A careful analysis of published systematic reviews is also helpful, as well as having a separate section for the review literature, since the primary literature describing individual patients may overlap with the clinical data found in a review article.

Clinical Experiences and Risk/Benefit Analyses

Clinical uses of the device outside a clinical trial or piece of clinical literature, may include customer complaints and use reports in publicly available databases, like the FDA's, the Medical Device Report, MAUDE, Warning Letters, Recalls, and Total Product Lifecycle databases.[7]

Although anecdotal information is not considered a reliable source for the CER, aggregates of individual experiences and uses are an important postmarket surveillance component of the CER requiring rigorous, reproducible, and reliable analyses to avoid bias.

A risk/benefit subsection is helpful to describe the device risks and benefits (including any residual risks identified in the manufacturer's risk mitigation activities, especially if they have not been identified elsewhere in the CER). Risks should be collected by the manufacturer and included in a risk management report which details all risks identified in both real (customer complaints) and theoretical engineering activities associated with failure modes and effects analyses.

Often, the clinical experience section of the CER is tightly focused on the risks associated with the device, so the risk/benefit subsection is an opportunity to compare and contrast all the known

Regardless of when the CER is first developed, it must evaluate all the clinical data available for the device to determine if the device is safe and performs as indicated under normal conditions of use.

The regulations do not state explicitly who is competent to write or review a CER, although scientific/medical prowess, clinical training, and experience writing a CER are required.

risks and benefits associated with the device. The goal is to document whether the benefits outweigh the risks of the device to the patient.

CER Conclusions

The author must determine if the clinical data demonstrate conformity to the Essential Requirements by showing the product is safe and performs as intended. A good practice is to answer the following questions in the conclusion of the CER:

- Are all clinical risks identified in the CER addressed in the risk management activities?
- Do gaps exist in demonstrating compliance to the Essential Requirements?
- Do gaps exist in the equivalence between the subject device and the other devices in the CER?
- Do the benefits outweigh the risks, and should the device continue to be used?
- Are more clinical data required to determine the clinical safety and performance of the device?

According to MedDev 2.7.1,[1] the evaluator should determine if the combined data demonstrate the device performs as intended and the device poses no undue safety concerns to either the recipient or end-user. The CER conclusion should enable the Notified Body and interested others to ascertain if pass/fail criteria have been met, if results and conclusions demonstrate compliance with the Essential Requirements, if certain device labeling claims are substantiated (by clinical data), and if the risk/benefit profile associated with the device use in humans is acceptable.

Conclusion

In summary, all medical devices require a CER prior to marketing in the EU, and developing each CER is a continuous process to be updated throughout the product lifecycle as the manufacturer learns of any changes affecting the risk/benefit profile of the device. CERs are increasingly useful in the U.S., because a robust CER will carefully summarize all clinical data available for a particular device from clinical investigations, clinical literature, and clinical experiences.

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Reshaping the Global Supply Chain for Investigational Biologics

PEER REVIEWED | Jonathan Calderwood

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Investigational biologics and biosimilars have always required special consideration and handling en route to clinical trial sites. Although the requirements have not changed over time, what has changed is that:

- these products are now so common they can no longer be considered exceptional compared to other types of investigational products; and
- the conduct of clinical trials has become a global activity.

It is not practical, or advisable, for sponsors and their supply chain partners to continue accommodating large molecules as rare, special cases. Rather, the industry must reshape its approach to the forecasting, packaging, and distribution of investigational products to make handling large molecules cost-effective, efficient, and compliant. Doing so requires working with partners who can develop and execute a strategy that spans the entire supply chain, encompassing both the physical and digital aspects of the drug supply.

Biologics are Special and Prevalent

Biologics (and biosimilars) are gaining share in research and development manufacturers' pipelines and becoming the norm in clinical studies. Consider these factors:

- Over the past decade, one-third of all new drug approvals has been for biologics.[1]
- In 2013, there were 907 biologics in development, targeting more than 100 diseases.[1] This is roughly 40% of all pharmaceutical products in the pipeline.[2]
- The worldwide pipeline includes more than 450 biosimilars and almost 400 biobetters, nearly all recombinant proteins or monoclonal antibodies, in development now.[3]
- By 2017, estimates are that seven of the top 10 pharmaceuticals worldwide will be biologics,[4] and that biologics' share of total pharmaceutical sales will approach 20%.[5]

Biologics remain "special" in terms of their shipping and distribution requirements. They are the high-maintenance "VIPs" of the clinical trials supply chain world; they also are expensive, costing, on average, 22 times that of small molecules.[6] Plus, they often have short shelf lives (compared to small molecules), and typically must be refrigerated (within a specific temperature range).

Supply Challenges are Magnified with Biologics

Sponsors and their supply chain partners must cope with the special characteristics of biologics and biosimilars in the face of increasing pressures and challenges within the clinical landscape. As they relate to biopharmaceuticals, these include:

- **The race to market.** The delay in getting a drug to market equates to anywhere from $600,000 to $8 million a day in lost revenue.[7] This urgency is intensified with biosimilars, where the first-mover advantage is pronounced. During the trial stages, the supply engine must hum along smoothly, without costly delays caused by preventable logistical snags.

LEARNING OBJECTIVE
After reading this article, participants should be able to explain the impact of biologics on the nature, design, and execution of global clinical trials.

DISCLOSURES
Jonathan Calderwood:
Nothing to disclose

With the increasing prevalence of biologics in the development pipelines, in comparative trials the expense of investigative materials plus the limited batch sizes means that a solution must be pursued to tightly control the quantities of inventory used.

- **Limited supplies.** Manufactured batches of biologics—both for the investigational product and any comparator products—are generally small, as manufacturing is more difficult and expensive. Thus, supplies must not be squandered and production must be carefully synched with demand.
- **The global footprint of trials.** Sponsors are turning to emerging markets for trial sites for a variety of scientific, practical, and economic reasons. About 45% of all clinical trials are conducted outside the U.S.[8] This patchwork of locations strains the mechanics of getting the right drug to the right patient at the right time, especially when the right drug is a biologic that must be maintained under certain physical conditions. Thus, companies must find ways to transport sensitive products safely and economically from one corner of the world to another.
- **Temperature restrictions.** Many biotech products need constant refrigeration to precise specifications, and regulators are now seeking proof that the cold chain has been maintained throughout the life of the product. Thus, companies need physical solutions (sophisticated shipping containers and experienced couriers) to maintain a cold chain, as well as digital solutions to provide proper end-to-end surveillance and documentation of the product's temperature.
- **Unpredictable patient enrollment.** The difficulties in finding eligible patients for clinical trials are well documented (and part of the reason that trials have become global). The challenge is exacerbated when the drug treats a niche population (as is often the base with biologics) or when patients must be treatment-naïve or biologics-naïve. Because recruitment rates are variable and difficult to predict—at the same time that biologics are expensive, not shelf stable, and have short expiration dates—sponsors must manage their supplies differently. It is impossible to manufacture 300% overage when a single kit could cost $20,000. Companies must have a way to match their production volumes to the current demand reality.

LEARNING EXAMPLE #1

A leading pharmaceutical company was 18 months into conducting a nine-year Phase III trial across 44 countries when it realized it needed to forecast demand more accurately.

The product characteristics and study protocol presented several challenges to the supply strategy:

- The investigational product had a short shelf-life.
- The dose could change at every patient visit.
- It was not possible to predict randomization at the site.

As a result, the sponsor had manufactured 100% overage for all dosage strengths and was providing all kit variations in the initial shipment to sites. A high percentage of kits were expiring before they were used.

The company sought the help of a supply chain specialist who could

- review the trends in dose titrations for patients enrolled in the study,
- extrapolate that demand to future visits of existing patients and projected patients, and
- generate a comprehensive demand forecast of patient need.

Based on the forecast, the manufacturing plan was adjusted so the amount of overage produced was reduced to 30%. Thus $4.9 million per year was saved in manufacturing and shipping costs.

The following solutions, having already been tried and tested in scores of trials, are quickly becoming established best practices within the industry. Although they are also recommended for trials of small molecules, they are critical in trials of biologics and biosimilars.

Demand Forecasting

With the increasing prevalence of biologics in the development pipelines, in comparative trials the expense of investigative materials plus the limited batch sizes means that a solution must be pursued to tightly control the quantities of inventory used.

Developing and maintaining an accurate forecast of product demand during a clinical trial is essential to satisfying the demand cost-effectively. The first step is to create a data collection plan that outlines which study variables (such as projected enrollment rates and product characteristics) will drive product demand. A baseline forecast is thus created to allow the sponsor to manage production runs, determine dispensing units and kit sizes, ensure that products are available when needed, and reduce waste from overproduction—all vital in managing the cost of biologic supplies.

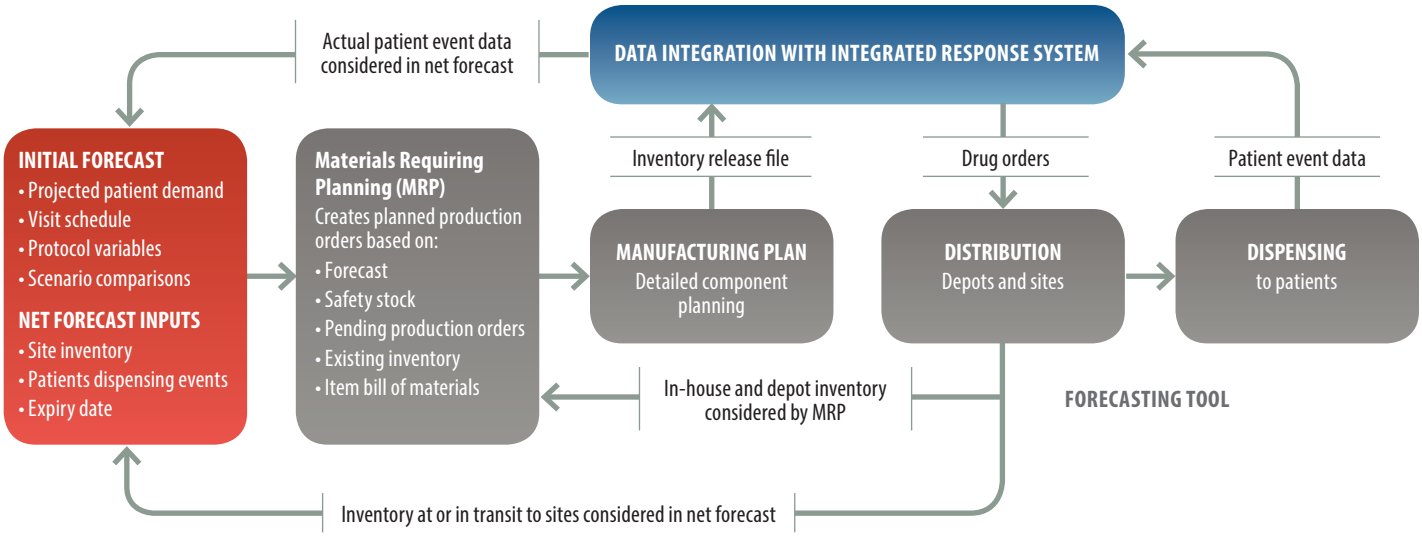
Then, during the study, with the right interactive response technology (IRT) in place, the baseline forecast can be continuously refreshed based on how demand unfolds. With real-time updates of what is happening throughout the supply chain, supply managers can be alerted to variances from the forecast and make real-time adjustments to demand forecasts (see Figure 1).

The key to optimizing both production and distribution in this way is having coordinated oversight of the entire supply chain.

Packaging and Labeling

Investigational products come in a wide range of formats, from syringes and vials to autoinjector pens and traditional small molecule tablets and capsules. Aside from the technology required to blind and efficiently automate the packaging process for trial materials, some strategies can

FIGURE 1: Supply Chain Management Data Lifecycle



conserve limited stock, such as specific designs of booklet labels for new entities, use of pooled inventory, and just-in-time labeling.

The options for product packaging and labeling need to be evaluated while the protocol is still under development, so the pros and cons of different formulations and kit designs can be considered. A vendor who brings experience across thousands of protocols and all therapeutic areas should be able to advise the sponsor on how to package and label the kits most cost-effectively, and how to use the kit design to encourage site and patient compliance.

The right partner can recommend methods that can save time and money in packaging biotech products, such as using just-in-time packaging and labeling or creating kit designs that take advantage of automation in the production line.

The key to realizing the benefits of a package and labeling strategy is to align it with the IRT functionality, so every aspect of production, distribution, and drug assignment is coordinated.

Optimizing Distribution

When distribution is optimized during a clinical trial, enough investigational product is on hand at sites to ensure continuity of care, having arrived in acceptable condition and with minimal cost. Achieving this ideal requires careful planning that begins when the protocol is still under development, and then continuous monitoring once the trial is in progress.

Developing a distribution strategy entails identifying the study milestones (such as the first patient in) that will affect product demand, and understanding all of the regulatory and logistical details that will affect delivery. A short list of such considerations includes:

LEARNING EXAMPLE #2

An emerging biotech company was planning a Phase II study, but was struggling with limited manufacturing capacity and could produce only small batches of the investigational product. The company had a tenuous ability to satisfy site and patient demands for both the investigational product and the comparator product during the first month of the study.

The original packaging plan consolidated seven weekly kits into one, which was going to put a strain on production capacity. The company's supply chain management proposed a new kit design and assignment schedule that addressed the issue. The new approach split the consolidated patient kit into three different assignments and spread the delivery to sites over a three-week period.

As a result, the sites could be seeded without risk of unblinding, and there was less likelihood of experiencing stock shortages. The simplified design meant that there was no need for a customized IRT, which saved $100,000 in addition to savings from a more efficient drug shipment strategy.

- The geographies
- Import/export regulations and timelines
- The number and mode of product shipments to sites and the related costs for storage and transportation
- Site inventory supply strategies
- The need for maintaining temperature stability
- The availability of comparator products
- The shelf-life of products
- Regulations concerning product return and destruction

With such information in hand, performing a thorough risk analysis and designing an optimal global clinical supply chain are possible. What will work best in any study depends on the protocol, how widespread the sites are, and which countries are participating. Also, a crucial requirement is a combination of both the data from the IRT and full clinical supply chain management, enabling a holistic view across the full program.

One particularly helpful step with biologics is drug pooling (i.e., sharing supplies across more

than one protocol). This can minimize the risk of a supply shortage, reduce drug waste, and reduce the amount of drug that must be stored at sites when sites are participating in more than one protocol.

Once the study has begun, the supply "engine" must conform to shifts in demand. Changes in the enrollment rate will affect shelf-life, expiry dating, and future packaging plans. Shipments must accommodate newly enrolled patients, subsequent visits, and a potential need for more replacement and safety stock.

Once enrollment winds down, the demand should be predictable, and the resupply strategy can be adjusted accordingly. With longer term demand projections, it may even be possible to reduce the frequency of drug orders. Then, as the study comes to an end, drug orders for the last patient drug assignments should consider the safety stock on hand at the sites.

Throughout the trial, the IRT system can serve as a window into study activity, providing real-time access to progress data and alerts at key junctures, such as impending product expirations, low stock levels, temperature excursions, and unacknowledged shipments.

Temperature Surveillance and Cold Chain Management

Once a study begins, companies must closely monitor temperature excursions that could affect inventory availability. Good distribution practices suggest that companies manage the temperature of product shipments from manufacture all the way to administration to patients. The watchwords are constant surveillance, traceability, and documentation, which can be applied in reality from the manufacturing stage to the clinical sites.

LEARNING EXAMPLE #3

A U.S.-based biotech company was conducting a five-year Phase III study with a high-risk population. The supply chain manager prepared multiple forecast scenarios for different study variables, and ultimately chose the scenario in which enrollment was projected to take eight months.

After recruitment began, it quickly became apparent that enrollment was ahead of the projection, and might be completed in six months. This accelerated enrollment, while overall a good thing, nevertheless would put a heavy burden on the bulk drug manufacturing and kit production.

Because a six-month scenario had already been evaluated, the sponsor had planned for this contingency, and the company was able to adapt swiftly. The company could keep the bulk production schedule in alignment with the need, and inventory levels never fell below a three-month supply. Over time, monitoring demand and adjusting the forecast resulted in a 23% reduction in the volume of long-term maintenance kits that needed to be produced.

LEARNING EXAMPLE #4

During a clinical inspection by the U.S. Food and Drug Administration, a major pharmaceutical company was advised to improve its tracking of temperature excursions so that monitoring extended throughout the life of the drug and notifications of excursions were more timely. The sponsor had been depending on its external partners to manage and report on excursions, and this lack of cohesiveness introduced the possibility that a drug that had exceeded its maximum allowable time outside the expected conditions might still be administered to a patient.

The sponsor adopted a comprehensive system to manage and maintain a drug's compliance to temperature specifications throughout the supply chain. The system collects temperature excursion data at the lot or medication identification level from manufacturer until the drug is administered to the patient. Data are recorded at such time points as the drug's production, storage, shipment from the manufacturer to depots, shipment to clinical sites, and receipt. The data are stored in a single database for analysis, so that temperature excursions can be readily adjudicated. The company's supply chain partners are notified of the need to replace any material that has exceeded its cumulative time out of controlled conditions.

The sponsor now receives a full historical record in a single, secure database of temperature data across the drug's life cycle within the study. This allows the company to remain compliant with regulatory requirements and to ensure that out-of-specification drugs are removed from the field and not administered to patients.

The ideal solution combines physical protection for the product (special shipping containers, handling instructions, and delivery services) with technology that records temperature and analytics that inform decisions. Using technology and consulting allows for end-to-end oversight with adjudication to aid speedier decisions of product and process compliance.

Getting it Right

The nature of biologics changes the way we must forecast, package, and distribute their related products in the clinical trial supply chain. Biotech sponsors need both the physical supply chain to deliver these sensitive drugs around the world, and an integrated chain of data to manage the process economically and to ensure compliance.

There is a significant interdependency between clinical supply management services and the interactive response technologies (such as interactive voice response) that are used to connect those clinical supplies with sites and patients. This interdependency becomes critical in trials involving biologics and biosimilars.

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Investigator-Initiated Trials (IITs)—A Primer for Physician Researchers for Conducting IITs

PEER REVIEWED | Surabhi Sharma, MSc, MS, MBA, CCRC | Steven Justice, MSc | Jennifer Christie, MD | Sita Chokhavatia, MD | Julio Polin

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Nonclinical (including *in vitro,* preclinical, and other) and clinical are the two major categories of investigational studies in drug development. Clinical trials may be sponsored by pharmaceutical, biotech, or medical device companies (industry-sponsored trials); by government, academic, or nonprofit organizations; or by a principal investigator (investigator-initiated trials [IITs]). In an IIT, the investigator has a dual role, serving as the sponsor-investigator (SI).

LEARNING OBJECTIVE
After reading this article, readers should be able to identify the differences in the responsibilities of the sponsor-investigator of an investigator-initiated trial, compared to those of an investigator or sponsor of a company-sponsored trial.

DISCLOSURES
Surabhi Sharma, MSc, MS, MBA, CCRC; Steven Justice, MSc; Jennifer Christie, MD; Sita Chokhavatia, MD; and Julio Polin: *Nothing to disclose*

Sponsoring a clinical trial entails numerous regulatory responsibilities; examples within the U.S. include those pertaining to the Food and Drug Administration (FDA) in the *Code of Federal Regulations'* sections 21 CFR 312 for drugs, 21 CFR 812 for medical devices, and 21 CFR 58 for preclinical trials. Similar regulations exist in the European Union (EU) and other areas. There is no "lite" version of sponsor responsibilities for SIs.[1]

From the regulatory perspective, an IIT cannot be sponsored by a company. The application must be unsolicited and made directly by the SI. However, a company can provide support to the SI in the form of investigational product (drug, vaccine, or medical device), analytical pharmaceutical ingredient, funding, a combination thereof, other support (nonmonetary services such as laboratory assays, pharmacokinetic analysis, etc.), or scientific and operational advice (as requested).

Although the SI's objectives may be purely scientific, a company may consider the study worthy of support if it satisfies one or more of the following conditions:

- Aligns with the company's strategy and IIT areas of interest
- Asks a significant scientific question supported by evidence from prior research,[2] has a robust study design, and has adequate sample size to answer the research question
- Fosters scientific exchange, collaboration, and innovation in medical research in pharmaceuticals or medical devices for government agencies, institutions, and other networks or individual investigators, leading to increased knowledge of the investigational product's efficacy and safety benefitting patients and healthcare providers
- Explores new indications, patient populations, dosage regimes, or combinations with other treatments
- Evaluates biomarkers that could be useful in developing new diagnostic tests or refining treatment management
- Demonstrates the company's willingness to expose its marketing claims to third-party research

TABLE 1: Differences in Responsibilities of a Sponsor-Investigator (SI) Conducting an IIT vs a Company Sponsor and an Investigator Participating in a Company-Sponsored Trial (CST)

Activities	Responsibility lies with:		
	SI of an IIT	Sponsor of a CST	Investigator Participating in a CST
Protocol design/amendments	☑	☑	
Operational execution planning	☑	☑	
Creating informed consent form	☑	☑	☑
Creating case report forms	☑	☑	
Compiling and filing of IND documents	☑	☑	
IRB/EC application and submission	☑	☑	☑
Arranging financial support for the study	☑	☑	
Managing investigational product supply (procurement, distribution, accountability, disposition)	☑	☑	
CROs/vendor selection and management	☑	☑	
Trial registration in public repository	☑	☑	
Site oversight and monitoring	☑	☑	
Arranging data and safety monitoring board safety review	☑	☑	
Safety reporting to regulatory authorities	☑	☑	☑
Safety reporting to the company	☑		☑
Safety reporting to all the sites	☑	☑	
Managing regulatory authority's audits	☑	☑	☑
Managing company's audits	☑		☑
Annual IND updates	☑	☑	
Regular update to financial supporters	☑	☑	
Data collection	☑		☑
Data management, review, and analysis	☑	☑	
Statistical analysis	☑	☑	
Study report preparation	☑	☑	
Results dissemination	☑	☑	
Study records' secure archiving	☑	☑	

In the U.S., 21 CFR 312 (and similar regulations and guidance in other countries) describes investigator and sponsor responsibilities in clinical trials (see Table 1). The SI's obligations include both those of a sponsor and of an investigator. Regulatory authorities define an SI as an individual, organization, or institution assuming responsibility for the initiation, conduct, management, and/or financial support of a clinical investigation.[3] The investigational product is administered or dispensed under his/her supervision.

Obtaining Company Support for IIT

Although the details for obtaining IIT support vary by company, the high-level process described in this article is standard in the industry (see Figure 1). Any new, unsolicited idea in the form of a proposal (concept/letter of intent/protocol) for an IIT should be submitted by the SI to the company, along with his/her curriculum vitae and an estimated budget for the trial.

The proposal must indicate what type of IIT support is required. Typical forms of support requested of the company for IITs include:

- Analytical pharmaceutical ingredient for preclinical IITs
- Investigational or marketed product, with label and packaging suitable for the trial (e.g., blinded or open-label)
- Placebo or active comparator, with label and packaging suitable for the clinical trial
- Financial support for specified activities
- Scientific and operational guidance on the protocol (if requested)
- Regulatory guidance in filing an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application
- Support for vendors/contract research organizations (CROs) responsible for site monitoring and data management
- Assistance with safety reporting processes (if requested)

Investigators should provide estimated timelines on when the study data would be available for publication or presentation.

Despite the frequency of some of the requests listed above, to ensure independence, companies do not provide input in the following activities associated with proposals:

- Protocol authorship
- Submissions to regulatory/health authorities
- Data collection or analyses

- Monitoring support of the IIT
- Assistance with subject recruitment
- Coauthorship or preparation, review, and validation of a scientific publication, unless otherwise outlined in the Clinical Trial Agreement (CTA) (i.e., limited right to review for intellectual property or confidential information disclosures)

Each company differs in its mode of receiving proposals. Historically, IIT submissions have been driven by face-to-face interactions between company's medical science liaisons with academic researchers. Although these practices continue today, many companies are moving to an electronic (automated) submission[4] via a webportal.

The company's IIT committee reviews the preliminary proposal for scientific merit, investigator expertise, alignment with the company's areas of interest, and the company's ability to provide the requested support. An IIT committee typically includes medical and scientific personnel, product and program trial managers, legal counsel, regulatory affairs representatives (U.S. or global), pharmacovigilance (safety) experts, and biostatistics experts as voting members. Nonvoting members consist of medical science liaisons, regional medical directors, marketing managers, patent attorneys, epidemiologists, health economists, and drug supply and packaging managers.

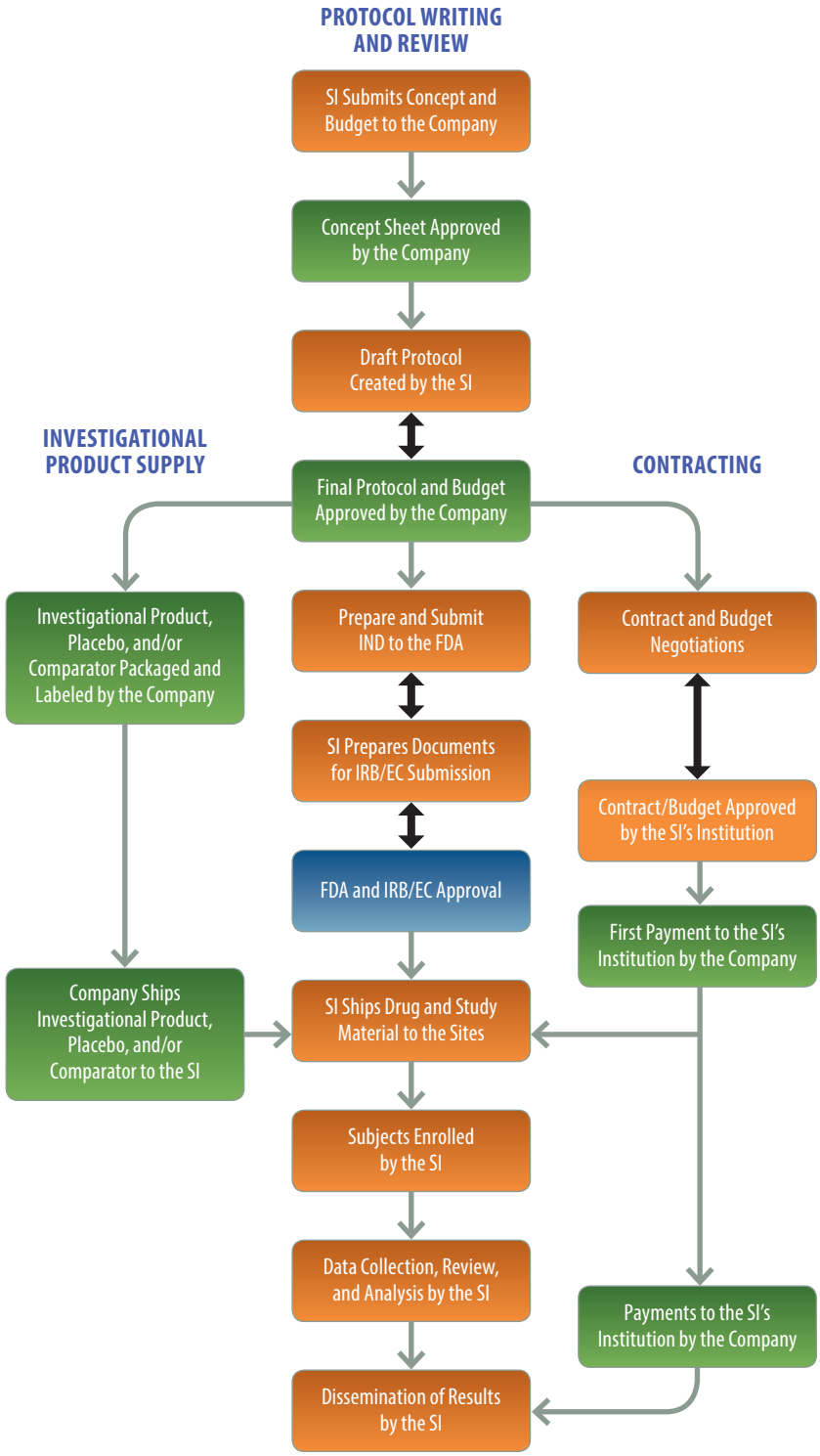
The IIT committee memberships may vary by company and according to the study reviewed; for example, for preclinical IITs, pharmacovigilance and regulatory affairs members need not be present. The committee's deliberations can factor in company strategy, but by law must not consider commercial (marketing) factors.

IIT support may not be offered or provided by a company as a kickback or discount; intent to promote any product; or intent to enable healthcare providers "experience" with a product.

On conditional approval, the committee will ask the SI for a full protocol and detailed budget within a specified time period, such as 60 to 90 days. The submitted budget will undergo an assessment against industry benchmarks, with some companies using commercial databases that provide fair market value metrics.[5]

The IIT committee reviews the complete proposal and budget again before the final decision. If the budget is above the industry benchmark rates, a lower budget amount may be offered. After full approval, the company's contracting department will contact the SI to finalize timelines, budget, payment schedule, and other support in a CTA.

FIGURE 1: Overview of the Sponsor-Investigator's Responsibilities in the IIT process



Upon completing the clinical study, the SI is responsible for final data monitoring, database lock, and submission of a clinical study report to the appropriate regulatory authorities and the company.

Since continuation of a company's support depends on study performance and achievement of project milestones, the SI and his/her institution should be aligned on timelines.

The following sections of an IIT CTA are areas of special focus for both parties:

- SI's duties
- Intellectual property and data ownership rights
- Publication policy/timelines
- Privacy (including matters related to the Health Insurance Portability and Accountability Act)
- Confidentiality
- Indemnification
- Payment schedule, specifying the final deliverable (final study report and/or manuscript)
- Serious adverse event reporting obligations
- Termination rights
- Return or destruction of used/unused study product/device by the institution

Subject injury is typically a smaller factor in an IIT CTA if the investigational product is already a marketed product. The company will not assume liability for a marketed product study over which it has minimal control; it will warrant that the investigational product is manufactured per specifications and conforms to the required quality standards.

Most companies order and package clinical supplies in parallel with CTA negotiations. Regulatory and customs approvals might be required before the investigational product can be shipped internationally, in which case the regulatory filing must be timed by the SI well before the shipment. Typically, the company takes responsibility for custom clearance for international drug supply and transportation.

If the study will be conducted at multiple sites, even though a company could ship directly to participating centers, it may prefer to ship only to the primary site, to minimize liability issues. In such cases, the SI will arrange further distribution of the investigational product from the primary site to all other study sites, while maintaining the temperature and shipping requirements.

Other Activities Required of the SI

STUDY STARTUP

The SI is responsible for preparing an IND/IDE package (or similar regulatory documentation required outside the U.S.) to satisfy each country's health authority. Approval of the IND/regulatory documentation from regulatory authorities is required before a clinical trial can be initiated.

The SI is also responsible for preparation and submission of the protocol and accompanying informed consent form for approval by an institutional review board (IRB) or an ethics committee (EC) to ensure subject protection (exception: preclinical protocols).

Further the SI must develop case report forms, subject diaries, and other data collection tools. If electronic setting up of these essential documents may require an experienced information technology professional, it will increase the overall study setup budgets. All documents should be ready and available either in paper format or e-format before study initiation.

Selecting and proper contracting with all the sites, laboratories, CROs, and other third-party vendors should be finalized in advance, so their services are available at study initiation. Contracts must outline any transfer of responsibilities from the SI to the contracted party according to 21 CFR 312.52 within the U.S. and other applicable regulations in participating regions.

STUDY EXECUTION

During the study, the SI is responsible for maintaining the investigational product's accountability, including shipment under required temperature and other conditions to the different sites, reconciliation of usage by subjects, and return of unused product.

If the company does not require the return of unused clinical supplies or medical devices, their destruction at the study center is usually based on institutional policies, and must be overseen or monitored by the SI.

The SI is also responsible for ensuring that his/her IIT is registered with ClinicalTrials.gov when conducted in the U.S., with the European Clinical Trials Database (EudraCT)[6] when conducted in the EU, and/or in other databases for other countries as appropriate.

MONITORING OBLIGATIONS OF THE SI

The tenets of good clinical practice and regulations from all health authorities require regular monitoring of studies to ensure their ethical conduct. This is the responsibility of the SI for an IIT.

In some circumstances, CROs may be contracted to support any or all of an SI's trial-related duties and functions.[7] The CRO would implement quality assurance and quality control activities, and would report irregularities to the SI. However, ultimately, the quality and integrity of the trial data always resides with the SI.[7] CROs may assist with updates to health authorities, and may be subjected to audits from the regulatory authorities, the SI's institution,

IRBs/ECs, and/or by the company supplying the product. Further, implementing quality assurance and quality control measures helps to ensure consistency in study conduct and data collection processes across all participating study sites.

In case of any protocol amendments, the SI also must manage the paperwork involved for resubmission to the health authorities and the IRBs/ECs. Protocol amendments must be resubmitted to the company's IIT committee for review, and to the IRB/EC for approval before implementing changes to the protocol.

Starting with the first administration of the product to the subject through the end of the follow-up period, the SI must continuously monitor the safety of the investigational product. Details of the subject safety monitoring must be outlined in the protocol and the CTA.

All adverse events (AEs) and unexpected fatal or life-threatening serious AEs (SAEs) associated with the use of a drug must be reported as soon as possible, but no later than required local regulatory deadlines to both the health authorities and the company. The CTA explains the timeframe for reporting SAEs to the company. Based on such information, the company may check its safety database for trends and disseminate information to investigators working on other clinical trials with the same investigational product. These notifications are issued in what is commonly referred to in the industry as "Dear Investigator Letters."

STUDY CLOSEOUT

Upon completing the clinical study, the SI is responsible for final data monitoring, database lock, and submission of a clinical study report to the appropriate regulatory authorities and the company. The SI also submits study closure notification to the IRB/EC and archives study documents according to the local regulations and CTA.

The SI should also update the relevant country registries for clinical trials (e.g., ClinicalTrials.gov, EudraCT). Finally, the SI will disseminate study results in an abstract, presentation, or publication to the company and to the broader scientific community. Encouragingly, sponsored IIT publications have been on the increase since 2012. An impressive 83% of IITs approved generate a publication.[4]

Harness IIT

Although there are many challenges to being an SI, success can be achieved by ensuring knowledge of all applicable regulations and accompanying responsibilities. Successful conduct of an IIT requires coordination between the SI, the company, and regulatory authorities, but leads to a variety of positive outcomes, including:

- Expanding scientific understanding of products and promoting innovative thinking
- Testing a potential idea that may support a new use/indication to benefit patients
- Generating awareness of products by disseminating new or supplemental data to the scientific and medical communities through publications
- Building or strengthening relationships with scientific experts and thought leaders

The results of these research endeavors fueled by the passion of the SI are invaluable for patients and physicians, and for the furthering of medical and scientific knowledge.

DISCLAIMER

The opinions expressed in this article are solely those of the authors and not necessarily those of their employing companies. The employing companies do not guarantee the accuracy or reliability of the information provided herein.

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HOME STUDY HS

Research "Outside the Box"

OPEN BOOK TEST

This test expires on August 31, 2016

(original release date: 8/1/2015)

Clinical Evaluation Reports for Medical Devices

1. What is a clinical evaluation report (CER)?

A. A written document about a clinical trial with a medical device

B. A written document about safety and performance of a medical device

C. A written document about complaints and experiences with a medical device

D. A written document about engineering risks of a medical device

2. Although the U.S. Food and Drug Administration (FDA) does not require a CER, what report is required in FDA submissions that has data similar to the CER?

A. Report of priors

B. Report of clinical study

C. Reports about risk management

D. Total product life cycle report

3. Why is a CER initially created?

A. To demonstrate conformity with essential requirements

B. To justify new drug studies

C. To satisfy venture capitalist groups

D. To support 510(k) submission

4. What is the name of the document providing guidance about the CER?

A. Essential requirements

B. CE mark

C. MedDev 2.7.1

D. Council Directive 93/42/EEC

5. What skills are necessary to write a CER?

A. Expertise in label review and report writing

B. Expertise as a clinical investigator and sponsor

C. Expertise in European and U.S. regulations

D. Expertise in research methods and device knowledge

6. What are the three types of clinical data to be included in a CER?

A. Clinical publications, abstracts, presentations

B. Clinical investigations, protocols, complaints

C. Clinical investigations, literature, experiences

D. Clinical information, indications, claims

7. What three characteristics should be considered when determining equivalence?

A. Clinical, biological, technical

B. Clinical, chemical, physical

C. Biological, chemical, physical

D. Biological, physical, technical

8. What type of clinical trial is considered the "gold standard"?

A. Observational trial with questionnaires

B. Patient-reported outcomes trial

C. Randomized, placebo-controlled trial

D. Registry trial with physician surveys

9. What type of literature is most appropriate for inclusion in a CER?

A. Single-author white paper

B. Peer-reviewed journal articles

C. Review article/editorial

D. Recent press release

10. What types of medical devices require a CER to demonstrate conformity with the essential requirements?

A. Only low-risk medical devices

B. Only high-risk medical devices

C. Only active implantable devices

D. All medical devices require a CER

Reshaping the Global Supply Chain for Investigational Biologics

11. What has changed over time to prompt sponsors to handle trials of investigational biologics and biosimilars differently?

A. Clinical trials are focused more on small molecules

B. Clinical trials are getting more standardized in format

C. Clinical trials have become global

D. Clinical trials only study biologics and biosimilars in small patient populations

12. According to *The New York Times* article "Biologics Boondoggle," on average, biologics cost about how many times that of small molecules?

A. 5 times

B. 10 times

C. 22 times

D. 30 times

13. Currently, on average what percentage of clinical trials are conducted in the U.S.?

A. 20%

B. 45%

C. 55%

D. 60%

14. Why do companies need digital/technological solutions for shipping and handling biologics?

A. To provide end-to-end surveillance of drug's temperature

B. To provide proof of delivery

C. To enable electronic sign off upon receipt

D. To ensure product stays within a designated sales market

15. Why should sponsors match their production volumes to current demand reality for trials involving biologics?

1. Biologics expire quickly

2. Patient enrollment is difficult to predict

3. Trial patients don't comply with treatments

4. Biologics are used to treat huge population volumes

A. 1 and 2 only

B. 1 and 4 only

C. 2 and 3 only

D. 3 and 4 only

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

16. **How can companies help forecast demand more accurately?**
- **A.** Create a data collection plan outlining study variables
- **B.** Project costs for marketing the drug if approved
- **C.** Estimate enrollment rates for trials of competing products
- **D.** Minimize packaging requirements

17. **How can baseline forecasts continuously be refreshed as demand unfolds in real time?**
- **A.** Supply managers should keep individual records throughout the trial
- **B.** Sponsor companies should update trial performance independently
- **C.** Relevant information on database should be updated weekly
- **D.** An interactive response technology should be implemented

18. **Why must companies evaluate options for biologic product packaging and labeling while the protocol is still in development?**
- **A.** To enable patients to have the choice of packaging to suit them
- **B.** To take into account different formulations and kit designs
- **C.** To select the cheapest option at an early stage
- **D.** To enable production operators to familiarize themselves with assembly

19. **During a study, how do longer term demand projections for the trial drug become possible?**
- **A.** The company uses historical data to reorder quantities
- **B.** Trial patients become more compliant with treatment throughout
- **C.** Quantity of trial drug is simply repeatedly ordered
- **D.** Once enrollment winds down, the demand becomes quite predictable

20. **What do good distribution practices suggest companies should do when shipping products?**
- **A.** Manage the temperature at manufacturing stage only
- **B.** Manage the temperature from manufacture to administration of patients
- **C.** Check the temperature at drug receipt only
- **D.** Check the temperature before administration to patient

Investigator-Initiated Trials (IITs)—A Primer for Physician Researchers for Conducting IITs

21. **An investigator-initiated trial (IIT) can be sponsored by a:**
- **A.** Pharmaceutical, biotech, or medical device company
- **B.** Government, academic, or nonprofit organization
- **C.** Sponsor-investigator
- **D.** Venture capitalist

22. **A company can support an IIT by providing its:**
- **A.** Drug, vaccine, or medical device
- **B.** CRA, biostatistician, or medical writer
- **C.** Laboratories, equipment, or facilities
- **D.** Medical science liaisons, marketing, or sales associates

23. **A company should NOT support an IIT to :**
- **A.** Expand scientific understanding of its product's efficacy and safety
- **B.** Test a potential idea that may support a new use/indication
- **C.** Expand the sales of its product
- **D.** Build or strengthen relationships with scientific experts and thought leaders

24. **In an IIT, the principal investigator has responsibilities of:**
- **1.** Sponsor
- **2.** Accountant
- **3.** Investigator
- **4.** Marketing specialist
  - **A.** 1 and 4 only
  - **B.** 1 and 3 only
  - **C.** 2 and 3 only
  - **D.** 2 and 4 only

25. **The concept for an IIT is submitted to a company via its:**
- **1.** Chief medical officer
- **2.** Medical science liaison
- **3.** IIT web portal
- **4.** Salesperson
  - **A.** 1 and 4 only
  - **B.** 1 and 3 only
  - **C.** 2 and 3 only
  - **D.** 2 and 4 only

26. **Continuation of the company's support to an IIT depends on:**
- **A.** Amount of kickback received by the company's employees
- **B.** Promotion of the company's product by the sponsor-investigator
- **C.** Prescription volume of the sponsor-investigator
- **D.** Study performance and achievement of project milestones

27. **Preparation of the investigational new drug (IND) application package for an IIT is the responsibility of the:**
- **A.** Company
- **B.** Sponsor-investigator
- **C.** Country's health authority
- **D.** Sponsor-investigator's institution

28. **Which of the following sponsor-investigator responsibilities can wait until the IIT is being executed?**
- **A.** IND approval
- **B.** Institutional review board approval
- **C.** Case report form and subject diary development
- **D.** ClinicalTrials.gov, European Clinical Trials Database, and/or other database registration

29. **Serious adverse events on IITs must be reported within the:**
- **A.** Local regulatory timelines
- **B.** Company-specified timelines
- **C.** Sponsor-investigator–specified timelines
- **D.** Study coordinator's convenience

30. **Conducting a successful IIT requires coordination between:**
- **1.** Sponsor-investigator
- **2.** Supporting company
- **3.** Regulatory authority
- **4.** Country's trade commission
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

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[DOI: 10.14524/CR-15-4078]

The Art and Science of a Symbiotic Relationship with Your Monitor

There are 68 National Cancer Institute (NCI)-Designated Cancer Centers in the United States and the District of Columbia that form the backbone of NCI's programs for studying and controlling cancer.[1] A typical NCI-Designated Cancer Center manages approximately 130 actively accruing therapeutic clinical trials, making the resulting volume of work enormous. With this diverse trial mix comes a multitude of sponsors in the form of cooperative groups, pharmaceutical companies, and consortiums.

Academic medical centers (AMC) with research teams engaged in these cancer studies offer a unique challenge by way of complex organizational infrastructure, which monitors must navigate. Monitors sent to AMCs may be familiar with an academic setting, but some may only have industry experience. Some monitors may have no experience at all with AMCs.

While monitoring experience differs from person to person, so does the approach individual monitors follow in reviewing documents. At the site level, staff members, in turn, must adapt to the variety of methods each monitor chooses to review the site's research documents. This dynamic, along with the volume of studies, makes it challenging to establish a symbiotic relationship, yet it is the key ingredient to successful trial outcomes.

Impact of Risk-Based Monitoring

In August 2013, the U.S. Food and Drug Administration (FDA) released industry guidance[2] on a risk-based approach to monitoring clinical trials. The guidance outlines multiple ways to monitor research, and is focused on preventing risk to data quality and human subject safety, and on ensuring clinical trial purity.

AMCs may encounter sponsors who use remote monitoring to supplement, rather than completely replacing, onsite monitoring visits. The resulting outcome is that the addition of remote monitors increases the workload of the overall monitoring plan.

At our AMC, we believe the focus should be on turning the collaboration with both our onsite monitors and remote monitors into a more constructive, successful, and efficient partnership. In the age of personalized medicine, our collaborations must be personalized as well, and it starts at the beginning of the study, from the very first subject. This is what AMCs can do quite well.

Laying the Groundwork

The time period between recruitment and treatment of the first subject is pivotal, and lays the groundwork for a fruitful site-sponsor relationship.

The first site visit is the best time to establish expectations and preferences, find common ground, and orient the clinical research associate (CRA) to the unique nature of the site. This is best done by demonstrating knowledge of the protocol, the site's standard operating procedures (SOPs), and, most importantly, the applicable federal regulations.

At this point, when a CRA is visiting our site, we review the SOP that establishes in writing when monitoring visits are scheduled, and with whom and how far in advance the visits need to be booked. Additionally, our SOP specifies the steps to be taken for responding to the follow-up letters that are required by our institutional review board.

We give this SOP to the monitor during the first monitoring visit associated with a given study. We also make sure to be familiar with the contract agreements and the sponsor's data entry expectations for the study.

At many sites, a study coordinator/clinical research coordinator (CRC) is the direct line of communication between the sponsor and the principal investigator (PI). Our model involves a CRC (who coordinates care and collects data) and data management personnel (who enter data), meaning there are two lines of communication to handle. We ensure that all monitors are made aware of this distinction in roles and responsibilities at the first visit, so that pertinent questions may be addressed in a timely manner.

Persistent and Consistent Efforts

In an ideal world, we would have study staff and CRAs who are experienced in both research and in oncology. However, in the real world, having these perfect combinations is not guaranteed.

Having an added perspective about each other's professional experience may be helpful in promoting increased collaboration. Our AMC works mostly on early-phase oncology clinical trials, where constant communication between the CRC and the monitor is crucial. This is especially the case since any decision to withdraw patients from treatment due to dose-limiting toxicities being reached is based on this two-way communication.

It goes without saying that being available for safety calls and timely response to e-mails has proven to be beneficial.

It is essential to approach this interface with a collaborative mindset, wherein both parties are to remember that the monitor plays on the same side as the site staff and that the monitor's only goal is to find fault. This is of particular importance to us at our site, since we are proud of the work we do and it is rather difficult to adjust to the idea of someone "checking" our work.

The best approach is to not get defensive, and to be amenable to feedback. We also need to make every monitoring visit productive by providing the monitor with necessary documents, charts, electronic access, time, and other resources that may be necessary to complete monitoring duties.

Conversely, the monitor needs to be cognizant of the fact that the study staff members have other studies and research subjects, and they cannot complete all requests at a moment's notice. Although we all want to be able to complete all tasks at the end of each day, all of us have had days when it is impossible. The onus is on us to convey an expected date of completion to the sponsor in a professional manner. If diplomacy isn't one's strong suit, getting help from a colleague or one's manager is advisable.

Another commonly encountered situation at AMCs is the attrition amongst monitors. In some instances, we have had more than six monitors in the course of a single study. Here again, effective communication with the new monitor on re-monitoring can preempt confusion and establish expectations.

Looking for Thought Leaders

Monitoring is a quality control measure put in place to ensure the integrity of trial data. It promotes the protection of study participants and ensures their rights are upheld. I have found that having a good relationship with my monitor makes sure that I capture the right data, at the right time, and in the correct format required by the sponsor—the first time around.

It is a widely acknowledged fact that sponsors want to work with PIs who are established thought leaders in their field. It is also necessary to acknowledge the role of the competent research staff at AMCs who are responsible for repeat business. Thus, mutual respect, open and honest communication, and real partnership between site staff and monitors will help facilitate successful study outcomes.

Monitors sent to AMCs may be familiar with an academic setting, but some may only have industry experience. Some monitors may have no experience at all with AMCs.

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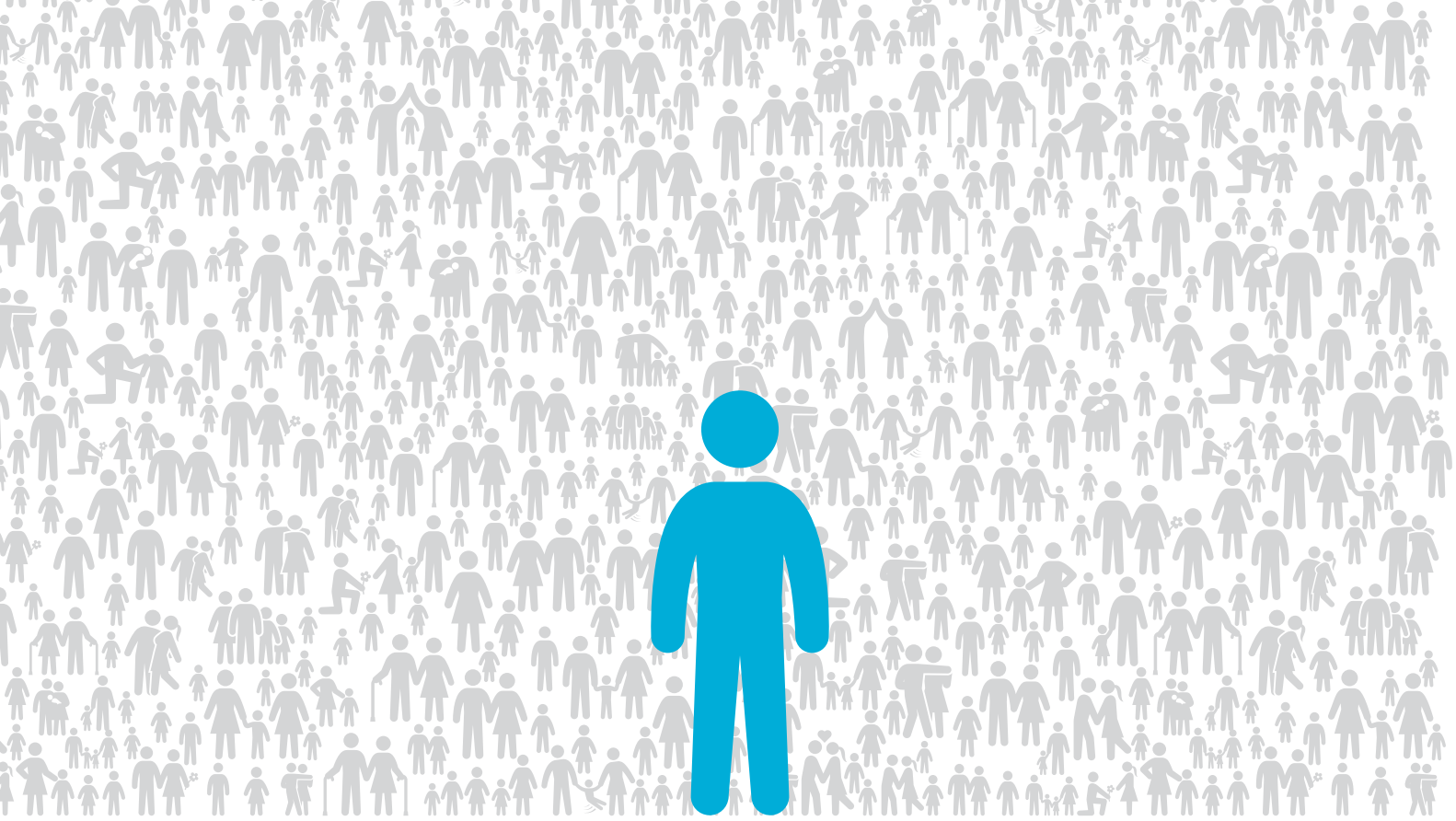


Personalized Medicine and Companion Diagnostics: *Shaping the Future of the Clinical Research Enterprise*

PEER REVIEWED | Heather Harris, MSc

[DOI: 10.14524/CR-15-0013]

The National Cancer Institute defines personalized medicine as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease."[1] Companion diagnostics are tests designed to assist in the decision-making process, developed ideally in tandem with a therapeutic product.[2]

Although the principles of personalized medicine—right drug, right dose, right time, right patient—have been around for some time, implementation has been limited by degree of understanding of the mechanisms of action of medicinal products and physiology of human response.[3] Others argue it is payers who are at the helm, controlling the market,[4] requiring evidence of better health outcomes for patients before loosening the purse strings.

The "one disease/one drug" paradigm just doesn't fit in today's complex landscape, as evidenced by diseases such as breast and colorectal cancers. In cancer therapy, information about a patient's tumor can be used to personalize treatment to better target tumor cells. For example, patients with colorectal cancer having KRAS (Kirsten rat sarcoma) wild-type tumors have a greater chance of responding to panitumumab therapy than those with KRAS mutation.[5] Once KRAS status has been determined, a personalized approach to therapy with products targeted to a patient's physiological and genetic makeup can be implemented, (i.e., the right drug for that patient). The advantages of personalized therapy, informed by companion diagnostics, in this instance a KRAS test, include both medical and financial aspects of not treating patients who do not stand to benefit and avoiding preventable adverse effects.

In the next decade, personalized medicine, informed and guided by companion diagnostics, in a niche-buster paradigm shift, will become the norm, if not the expectation.

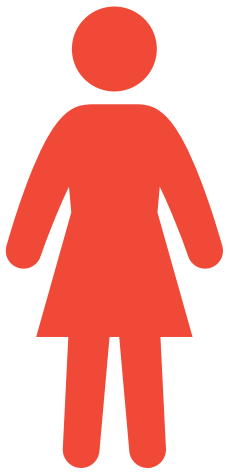
Heterogeneity: One Size Does Not Fit All

The next decade will bring a stepwise approach to personalized treatment, where patients are stratified into groups that share biological characteristics (so-called "stratified medicine").[3]

Historically, cancers are classified by site of origin (e.g., colorectal or breast). It is becoming more common to see diseases as heterogeneous, subdivided into categories based on metabolic profile, as seen with colorectal cancer and KRAS gene status. Breast cancer presents a similar example in which at least three subtypes are recognized: HER2 positive, ER/PR positive, and triple negative.[3]

Once the pathophysiology of the tumor is identified and understood, treatment, or access to clinical trials, can be tailored to maximize opportunities for a successful outcome for the patient. This informed approach should end the trial-and-error tactics commonly seen, where first-line approach is tried and tested, followed by second-line, if that fails.

The "one disease/one drug" paradigm just doesn't fit in today's complex landscape, as evidenced by diseases such as breast and colorectal cancers.



The Evolution of Breast Cancer Therapy

Perhaps the first evidence of personalized medicine coupled with a companion diagnostic was released in 1976, when Lemer et al.[6] reported on the utility of estrogen receptor assay results and patient response in women with breast cancer treated with tamoxifen. In the 1990s, HER2 positive tumors were targeted with monoclonal antibody therapy, and in the current decade, patients with BRCA1 or 2 mutations are testing a new specialized inhibitor.[3]

The evolution of breast cancer therapy is an example of medicine moving from a one-size-fits-all (or doesn't) approach to stratified medicine, edging on a personalized, genomic approach to treatment informed by companion diagnostics.

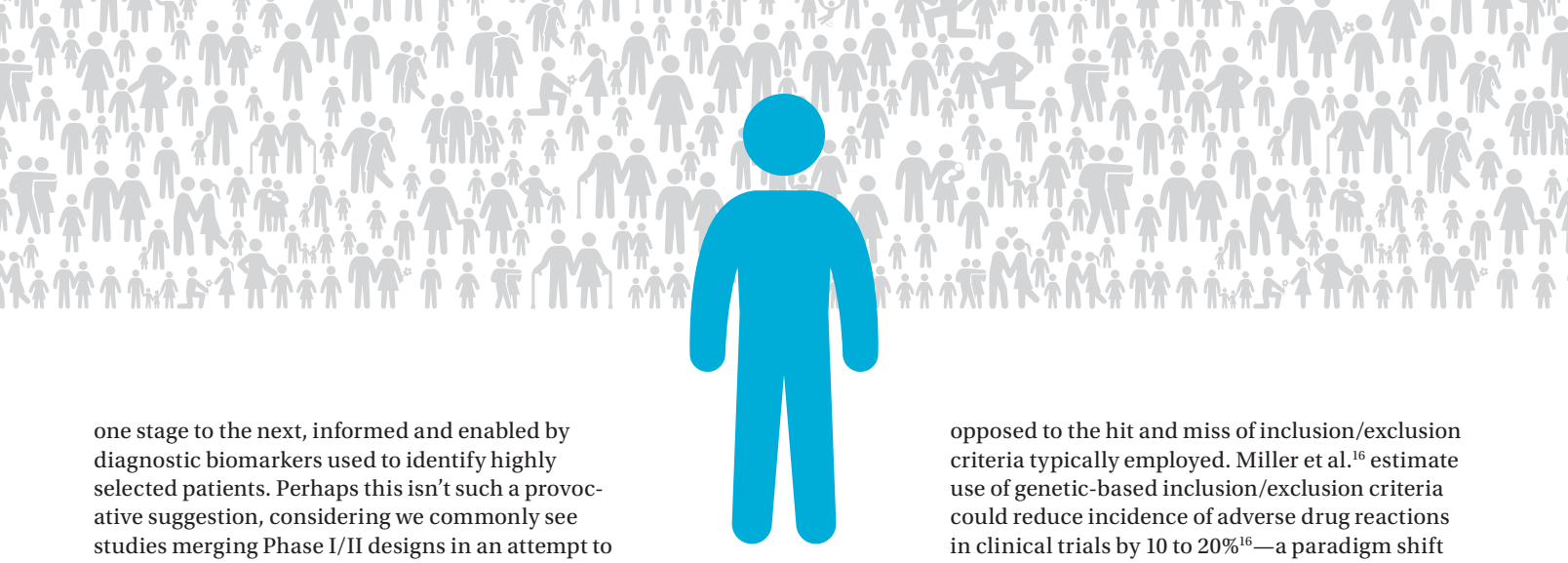
Dahiya[7] predicts, "It will be possible to predict susceptibility to diseases with precisely chosen medicines, therapies, and customized lifestyle advice." This approach will have significant effects on clinical development and healthcare, moving from a sick-care system to a truly healthcare and preventive system, enabling patients and their physicians to reach better outcomes.

Evidence of the impact of companion diagnostics in medicine has been seen mainly in oncology; however, other therapeutic areas are catching up. Within the spectrum of infectious disease, treatment of patients with HIV/AIDS must undergo tropism testing to identify those with CCR5-tropic HIV-1 to guide therapy with maraviroc.[3]

Walking a New Trial Landscape

Personalized medicine will reshape inclusion/exclusion criteria for clinical trials. Clinical biomarkers will be used to identify those who stand to benefit most from therapy, or conversely, exclude those who would never benefit (i.e., screening out protective genotypes).[8] This approach will reduce sample sizes, shorten overall trial duration,[9] and speed the pathway to regulatory approval and getting the product into the hands of patients.

Arlington[10] predicts the traditional Phase I through IV clinical development pathway will merge into one adaptive trial, evolving from



one stage to the next, informed and enabled by diagnostic biomarkers used to identify highly selected patients. Perhaps this isn't such a provocative suggestion, considering we commonly see studies merging Phase I/II designs in an attempt to speed the path. A search of the ClinicalTrials.gov database identified more than 12,000 studies of such design.[11]

THE REGULATORS

Through a guidance document issued in 2011, the U.S. Food and Drug Administration (FDA) recommends co-development and simultaneous approval of targeted therapeutics and their companion diagnostic, as does the European Medicines Agency (EMA) and the Japanese authority.[2] FDA has taken the bold step of advising developers not to bother seeking regulatory approval unless they are applying this approach.[4] In the foreseeable future, companies will probably follow the likes of Roche and a handful of others, incorporating companion diagnostics into their clinical development strategies.[7]

THE PAYERS

With prescription drug costs estimated to exceed $260 billion USD in 2012,[12] payers have a vested interest in cost containment. A more selective, personalized approach to therapy would significantly increase the value proposition to payers. It limits access of expensive new therapies to those deemed most likely to benefit, backed by evidence[4] and containing costs.

In a survey conducted by Cohen, Wilson, and Manzolillo,[4] 83% of respondent payers felt it was within their rights to limit reimbursement of certain drugs to patients with evidence to support reasonable potential for benefit (e.g., companion diagnostic–based evidence).

The Institute of Medicine estimates the medical cost of adverse events at $3.5 billion annually in the U.S.,[13] a massive burden on the healthcare system. A personalized approach to therapy could reduce this burden.

THE PATIENTS

At the core of personalized medicine are the patients who stand to be the clear beneficiaries. Drug efficacy rates range from 25% in oncology products to 80% with analgesics.[14] However, with today's previously unheard-of level of therapeutic precision, patients can be selected for clinical trials of therapies, based on molecular biomarkers[15] as opposed to the hit and miss of inclusion/exclusion criteria typically employed. Miller et al.[16] estimate use of genetic-based inclusion/exclusion criteria could reduce incidence of adverse drug reactions in clinical trials by 10 to 20%[16]—a paradigm shift that would be of great benefit to patients.

> In the next decade, personalized medicine, informed and guided by companion diagnostics, in a niche-buster paradigm shift, will become the norm, if not the expectation.

A New State of Equipoise?

Genetic biomarkers have already altered the face of the Phase III clinical trial[17] by allowing study teams to make recruitment more targeted. The concept of molecular medicine may alter the hierarchy of evidence. Historically, at the top of the hierarchy is the prospective randomized controlled clinical trial. The highest quality of data to support approval and use of new therapies must come from this highly regarded mechanism. However, evidence to support use of a molecular-based diagnostic test may be the product of laboratory-based research using archived biospecimens, perhaps sourced through clinical trials.[17] Data from research on these specimens may provide convincing evidence a particular biomarker would be selective for patient response to a particular drug. This information destroys the state of clinical equipoise critical to the ethical initiation of a prospective clinical trial.[17]

Initiating a Phase III trial already knowing what patients' responses will be would be unethical, not to mention impossible to move through research ethics approval and recruitment. Will we see a new level of respect for molecularly based, retrospectively acquired data?

Staring Down Four Big Hurdles

Uncommon Partnerships: Co-development may require partnerships of unnatural partners (i.e., pharmaceutical companies and diagnostics companies), who may have different strategic objectives, cultures, and operating principles. For example, Pfizer and Abbott Molecular forged a partnership in the co-development of a diagnostic for the analysis of ALK in non–small cell lung cancer tumor tissue for Pfizer's Xalkori.[18]

The development and approval course proved a test of the union, subject to delays and challenges brought about by misaligned priorities, but subsequently resulted in a regulatory approval.[18] The next decade will bring more of these uncommon partnerships, in an effort to regain position in the new research enterprise.

Contract Research Organizations: Despite guidances from the three main global regulatory bodies (FDA, EMA, and Japan) supporting contemporaneous development and approval of companion diagnostics and therapeutics, this territory is novel to most developers and contract research organizations (CROs). In 2012, few CROs held significant experience in companion diagnostic development and negotiating the pathway to regulatory approval.[18]

Regulatory Affairs: Therapeutics and companion diagnostics fall within different divisions at FDA, further complicating the development pathway and requiring careful coordination from development to submissions.[19] Here lies a tremendous opportunity to truly enable personalized medicine.

Financial Barriers and Reimbursement: Drug development has historically been an industry of failure, with compounds having a 1 in 10,000 chance of successfully navigating the pathway to market.[20] Estimates suggest companies spend as much as $5 billion USD getting one drug to market, when factoring in cost of failure.[21] Co-development increases the complexity of the development pathway and associated financial risks, presenting an uncertain case for the leaders of some diagnostic companies, who are perhaps less willing to share the financial risks.[18]

Medicare, the largest payer in the U.S., reimburses based on cost, not considering complexity of testing, value, or potential savings to the system.[22] If co-development of a therapeutic and companion diagnostic will require the same evidence-based pathway as a new drug, cost structures need to better align to foster continued innovation—a seismic shift to the current reimbursement paradigm. This seismic shift will only occur with concrete evidence of cost savings, and linkage of cost categories within the system.

The New Marketing Landscape

Companies like 23andMe have pushed the boundaries of marketing personalized medicine, occasionally resulting in FDA sanctions.[23] Personalized medicine brings with it a plethora of medical, legal, ethical, and regulatory issues that the clinical research enterprise is struggling to catch up with.

When companies commence direct-to-consumer advertising, bringing genetic testing to the living rooms of Americans, one may expect a spate of potentially inappropriate testing. Or it could have the opposite effect, empowering consumers to seek medical advice or clinical trial opportunities.

Personalized Medicine Act?[24]

To foster continued innovation in personalized medicine, Jenkins[25] advocates for incentives for developers, similar to those seen in the Orphan Drug Act in the U.S., which has interesting parallels to personalized medicine (i.e., substantially smaller markets of less than 200,000 for an orphan drug with potentially smaller return on investment).

The Orphan Drug Act exists to foster development of products for rare diseases and offers accelerated regulatory review combined with greater market exclusivity.[26] A similar system could enable the personalized medicine enterprise.

In the European Union, protocol assistance and financial incentives foster development of orphan drugs.[27] FDA offers financial assistance for clinical studies of orphan products.[27] Considering 50% or more orphan diseases have a genetic component, categorizing personalized medicine products as orphan drugs is logical.[27]

According to Hughes-Wilson,[28] several personalized medicines carry market potential within orphan drug categorization (e.g., approximately 23,000 patients were treated with Gleevec in 2005).

Hold On to Your Hat

The clinical research enterprise is poised to undergo a dramatic revolution over the next decade. Decoding the human genome opened the door to a new paradigm in development in terms of a personalized approach to therapy informed by companion diagnostics—an evidence-based approach to drug development. In one recent example, Health Canada approved two therapies for metastatic melanoma, both requiring patients undergo a validated test for the BRAF V600 mutation.[29]

To fully embrace the revolution requires uncommon partnerships, equitable reimbursement structures, and an enabling regulatory framework to reach from development to market. Into the future we go.

This brand of informed approach could spell the end of wasteful trial-and-error tactics.

We won't be able to leverage this sea change without a new breed of partnerships, reimbursement structures, and an intelligent regulatory framework.

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OPINION

Geriatric subjects are unique from other populations involved in clinical research because chronological age alone reveals little about a person's health or capabilities.[1] There is no single trajectory through old age; while some people become frail in their 50s, some 80- and 90-year-olds dance, play softball, and perform on synchronized swim teams.

Lessons Learned: Recruiting and Retaining Geriatric Subjects

PEER REVIEWED | Sandra Mutolo, MSW, LCSW

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Although people age 65 and older are the fastest growing segment of the United States and European populations, they are not well represented in clinical trials. A 2011 review of 109 clinical trials found that 22% excluded patients based on an upper age limit.[2] Almost half of these studies used exclusion criteria for a range of conditions that primarily affect older people, such as cancer, heart disease, kidney disease, diabetes, and congestive heart failure. As a result, treatments developed for elderly people may not be suitable for the people most likely to use them.

Prepping for Older Subjects

My experience as a clinical research coordinator on trials for Alzheimer's patients and other geriatric populations has taught me several valuable lessons in recruiting and retaining these subjects. Most important is the flexibility and advanced planning required to address the wide range of abilities and contingencies of an aging population.

Clinical research with older adults presents a variety of challenges, such as:

- cognitive deficits
- fatigue
- sensory deficits
- mobility issues
- transportation problems
- caregivers as co-participants

The remainder of this article addresses considerations to factor into the conduct of clinical trials related to each of these issues.

COGNITIVE DEFICITS

Although cognitive impairment is not a normal part of aging, it is more prevalent among the elderly, and the incidence increases as age advances. Unlike other vulnerable populations, such as children or pregnant women, there are no specific regulations that govern research with cognitively impaired participants.

Cognitive deficits in research subjects present several issues, foremost among them the capacity to give informed consent. Determining capacity to consent is left to the judgment of the principal investigator. Assent to participate in a study is an important safeguard for these subjects because people with cognitive impairment may be more vulnerable to coercion.

Treating all individuals with cognitive deficits as incapable of understanding their role in a research project is inaccurate and disrespectful;[3] each potential subject must be assessed for capacity to give consent to participate in the study. Those who cannot consent on their own must have a consent signed by a legally authorized representative. Further, patients who can give consent at the outset of a study may require a proxy consent if their capacity changes during the study.

FATIGUE

Elderly subjects with multiple co-morbidities or cognitive deficits may be more prone to fatigue. Researchers must pay attention to the pacing of the study and to any signs of fatigue or agitation among participants. Adaptive approaches, such as taking breaks, offering reassurance or gentle encouragement, providing snacks, and/or changing the order in which tests are administered, may be helpful.

Sometimes, subjects with cognitive deficits may find study instruments or portions of the instruments difficult, if not impossible to complete, leading to frustration and agitation. For some patients, the best approach is to leave those instruments to the last or eliminate them entirely.

SENSORY DEFICITS

Vision and hearing problems are common in older adults. It is always preferable for subjects and caregivers to bring their own adaptive equipment to study visits; however, having large print materials, magnifiers, and writing aides (e.g., grips for pens or pencils) on hand is helpful.

Hearing aids are critical to the success of study visits for subjects with hearing impairment. Amplification systems are available, but some clinical teams have mixed success in using them. Reminding subjects and caregivers prior to study visits to wear their hearing aids will help sites avoid rescheduling hassles.

Geriatric subjects are unique from other populations involved in clinical research because chronological age alone reveals little about a person's health or capabilities.

RESOURCES

Alzheimer's Association
https://www.alz.org/care/alzheimers-dementia-caregiver-stress-burnout.asp

Area agencies on aging
www.aoa.gov/AoA_programs/OAA/How_To_Find/Agencies/find_agencies.aspx

Cognitive capacity and informed consent
http://grants.nih.gov/grants/policy/questionablecapacity.htm

Elder abuse information
www.ncea.aoa.gov/faq/index.aspx

Eldercare locator
www.eldercare.gov/Eldercare.NET/Public/Index.aspx

Help guide
www.helpguide.org/articles/stress/caregiving-stress-and-burnout.htm

State-by-state resources
www.ncea.aoa.gov/Stop_Abuse/Get_Help/State/index.aspx

ADDITIONAL READING

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MOBILITY

The accessibility of the study site and the convenience of its layout are important factors for subjects with mobility problems. Consider the proximity and accessibility of restrooms in the facility when deciding where to hold study visits. Restroom facilities should be large enough to accommodate the subject and caregiver. Having a wheelchair on hand is helpful, especially if subjects will need to walk a distance.

TRANSPORTATION PROBLEMS

Elderly subjects and their caregivers may no longer drive or may drive only short distances. Arranging transportation and offering home visits are pivotal to reaching recruitment goals and retaining subjects. A caregiver's or patient's increasing frailty or deteriorating vision can often result in requiring help to get to study visits or a switch to home study visits.

CAREGIVERS AS CO-PARTICIPANTS

I was once involved in a prospective study of wandering behavior in veterans with mild dementia that required the recruitment of 154 patient/caregiver dyads. Two amendments to the protocol were necessary to enable the team to meet this goal.

First, the inclusion criteria initially called only for caregivers who lived with subjects. Because the study involved patients with early dementia, several potential subjects still lived alone, but had caregivers who provided ongoing care and who were willing to participate in the study.

Another requirement was that the dyad maintain the same caregiver throughout the two-year study. Sometimes the original caregiver became unavailable to continue in the study, so allowing for alternate caregivers enabled the research team to identify other family members or friends who would serve as partners and continue the veteran's participation in the study.

Further, the team found using certain terms proved problematic in recruitment efforts. Many prospective patients did not acknowledge having memory loss and were distressed by the term "dementia" in the study title. When discussing the study with potential subjects, we opted to use "mild memory problems" instead.

We also discovered that family caregivers resisted the word "wandering" when discussing or describing their family member's behaviors. Caregivers would often respond, "He's not that bad off" or "She's not a wanderer." In recruiting dyads for the study, the team used other terms for describing wandering behavior, such as "becoming

lost or separated from caregivers" or "becoming disoriented or unable to find his or her way."

Some solutions we found in working with caregivers included the following:

- Offering after-hours visits increased our subject pool because employed caregivers were usually unavailable during regular business hours.
- Having books, videos, crayons, and washable toys available was helpful when caregivers brought children or grandchildren with them to the study visits.
- Allowing for flexible scheduling meant caregivers and patients with multiple appointments could schedule visits around them, reducing the drain on their time and increasing their willingness to participate.
- Being proactive was an important tool in keeping subjects enrolled, because the attrition was higher than the 40% anticipated in the protocol (e.g., telephone calls between study visits allowed us to track adverse events and stay abreast of changes in the subjects' living circumstances, such as changes in caregivers, planned moves, or extended travel).
- Providing subjects and caregivers with a notebook helped to outline study procedures and offer information on what to do if they were out of town for an extended period, moved, became ill, or were hospitalized helped retain participants.

Caregivers for frail elderly people, especially those with dementia, have high levels of stress, and they often need supportive services. Visit the websites in the sidebar for more information. Further, patients with these conditions are more vulnerable to abuse, neglect, and exploitation. Recognizing these trends, the team kept a list of telephone numbers and websites for referrals to local community resources. The Administration on Aging provides national referrals through a toll-free number (800-677-1116) to resources including home-delivered meals, adult day care, and in-home services.

Every state has laws that govern the reporting of elder abuse or the abuse of disabled adults. Subjects exhibiting signs of abuse, neglect, or exploitation should be reported to a local agency. Web-based resources are listed in the sidebar.

Looking Forward

Despite a growing awareness of the limited numbers of older adults enrolled in clinical trials, even for diseases that primarily affect the elderly, under-enrollment for this group persists. As our population ages, it is critical to ensure that treatments developed through clinical research are effective and appropriate for older adults. Research with elderly subjects presents several challenges, but they can and must be addressed.

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ETHICALLY SPEAKING

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To Check, or Not to Check? Or Uncheck?

The box, that is. We are referring to the box next to the questions on the Federalwide Assurance (FWA)[1] form that asks if the organization providing (and the individual signing) the form agrees to apply the assurance to all human research, regardless of funding source. (There are actually two boxes, one for all Subparts and one for Subpart A only. For this column, they are referred to together as "the box.")

Some background: Any organization receiving support for human research from the U.S. Department of Health and Human Services (HHS) or any of the federal agencies that have agreed to the Common Rule must file an FWA, which provides assurances to the government that the organization will follow the HHS rules in the *Code of Federal Regulations* (45 CFR 46). Among the organizations with an FWA are academic medical centers (AMCs) and hospitals that conduct federally supported human research, including those participating in any of the cooperative oncology groups, or are subcontracted to an AMC for a federally funded clinical trial or other human research study. Even standalone clinical research sites are required to file an FWA if staff at the sites participate in federally supported studies.

Who's Watching Whom?

Organizations with an FWA are under the oversight of the Office for Human Research Protections (OHRP), based within HHS. Under the regulations, OHRP has jurisdiction over research that is conducted, supported, or otherwise subject to regulation by a federal department or agency that has adopted the Common Rule. Support can be in the form of funding or nonmonetary support, such as HHS providing equipment or central lab services without any exchange of money.

Institutions are allowed to check a box on the FWA that cedes oversight to OHRP for all human research, regardless of federal support. In such cases, OHRP has oversight because the institution has volunteered its research to be "otherwise subject to regulation."

For example, if your institution has checked the box, then a typical industry-sponsored multicenter clinical trial falls under not only U.S. Food and Drug Administration (FDA) oversight, but also under OHRP. If there is a reportable incident during the trial, such as an "Unanticipated Problem Involving Risks to Subjects or Others," or if the study is terminated/suspended by the applicable institutional review board (IRB), or if there is serious or continuing noncompliance, reports must go to *both* agencies.

Similarly, a person could contact OHRP and make allegations about the study/investigator/IRB. OHRP can choose to investigate any of these matters, and depending on the results of the investigation, take further action independent of, or in addition to, FDA's actions. Organizations that have undergone this dual oversight can suffer considerable costs in terms of the time, expense, and effort of responding to an OHRP inquiry or investigation of a research study, whereas if the box was not checked, OHRP would have no authority to conduct an inquiry or investigation.

It should be noted, however, that an informal review of compliance letters published by OHRP on its website suggests that, in recent years, it has elected to limit enforcement activities to HHS-funded research.

Who's Checking What?

According to the Association for the Accreditation of Human Research Protection Programs (AAHRPP®),[2] 63% of all FWAs have boxes checked. On the other hand, of AAHRPP-accredited organizations, only 36% are checked.

This difference underscores the rationale for why some institutions continue to leave the box checked. On one hand, checking the box provides a clear statement that the institution has a single standard for the protection of human subjects for all its research, rather than a double standard that provides one set of principles for federally funded projects, and a lesser standard for all other research.

However, because AAHRPP-accredited institutions have a Human Research Protections Program (HRPP) single standard based on AAHRPP requirements, checking the box is not considered necessary. The institution does not need to fall back on the regulations as an excuse to conducting ethical human research. Yet, as noted by *IRB Advisor* in 2013,[3] the regulatory burdens that are associated with checking the box are substantial, and with or without AAHRPP accreditation, organizations can develop an HRPP based on a single standard and hold to it, without opening themselves up to the scrutiny of OHRP for non–federally funded research.

So why haven't all institutions that previously checked the box, now uncheck it? Some institutions have a good reason: For example, some legal counsels interpret state law (e.g., New York, Virginia) to put additional regulatory requirements on institutions that don't check the box, and many institutions have calculated that the burdens of OHRP oversight are preferable to those associated with scrutiny by the state. Presumably, most of the others have not developed a formal HRPP, and thus do not yet understand the benefits of unchecking the box.

And Don't Forget…

Should your institution decide to uncheck the box, be advised that OHRP oversight still holds for research approved during the time the box was checked, and it can take some time, even years, before the research is complete.

Institutions are allowed to check a box on the FWA that cedes oversight to OHRP for all human research, regardless of federal support. In such cases, OHRP has oversight because the institution has volunteered its research to be "otherwise subject to regulation."

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Optimizing Postmarket Surveillance Reports: *A Medical Device Focus*

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When designing a medical product, manufacturers must ensure the benefits outweigh the risks to the patient. Companies often have internal, confidential methods to gather postmarket surveillance data; however, not all of that important user information is reported directly to the company.

The U.S. Food and Drug Administration (FDA) requires comprehensive reporting of product problems, adverse events, and other information which is stored in publicly available databases. The European Union (EU) obligates medical product manufacturers to report to the governing body any adverse events causing potential patient death or serious injury; however, this information is stored in a comprehensive, but not publicly available, database.[1] The data in these and other databases are used to analyze the benefits and risks of a product.

Several regulations, guidelines, and international standards describe how to analyze postmarket surveillance data and to conduct risk/benefit analyses. The Medical Device Directives 93/42/EEC (for medical devices), 90/385/EEC (for active implantable medical devices), and 98/79/EC (for *in vitro* diagnostic medical devices) describe the regulations for medical devices in the EU, and the Medical Device Directive (MedDev) 2.7.1 provides a guideline for analyzing medical device clinical trials, clinical publications, and clinical experiences in a clinical evaluation report.

Further, EN ISO 14971:2012 from the European Committee for Standardization (CEN) describes a regional standard for medical device risk management (i.e., to identify, evaluate, control, and monitor the effectiveness of the risk controls associated with medical devices). Clinical evaluation reports, clinical risk/benefit analyses, and risk management plans are common tools used in the medical device industry, and all of these rely on postmarket surveillance data during the life cycle of the product.

This article describes how to use online databases to find postmarket surveillance data, the information accessible within each database, and how to integrate the data into the appropriate postmarket surveillance report.

How to Develop the Search Protocols

Internal postmarket surveillance processes alone can sometimes miss risks and benefits, rare adverse events, long-term effects, or general problems with the entire product class. Information from publicly available databases including clinical literature, adverse events, recalls, FDA Warning Letters, total product life cycle (TPLC), similar devices, and clinical trials can all be leveraged to evaluate the risks and benefits of a product.

A good process is to use a rigorous, systematic search protocol with careful documentation of all search terms and all inclusion and exclusion decisions. This builds a comprehensive, relatively unbiased picture of the postmarket surveillance data for the product.

Slight variations in search steps may be helpful when searching specific databases (e.g., searching by product code in the TPLC database, which combines data from various FDA sources, will be more comprehensive than searching by device name). These variations should be detailed in the postmarket surveillance search protocol, to ensure the boundaries of the searches are clear. In addition, the answers to some of the following questions may help to shape the search parameters in the protocol:

- Will the searches include only the specific device, or will members of a device family be included?
- Will any instruments or accessories be included?
- Will the searches focus solely on a particular indication for the product, or will multiple indications for use be included?
- Will equivalent (or similar) devices be included?
- What problems are known and associated with the product?
- How many recalls have been issued for the product, and what were they about?
- What types of data will be included or excluded?

The protocol should explain how to prevent "cherry picking," and how to ensure all data (both good and bad) are included in the report.

For example, two studies[2,3] described systematic searches in the U.S. FDA Manufacturer and User Facility Device Experience (MAUDE) database to identify adverse events and device failures of the da Vinci Surgical Robot. Manoucheri and colleagues[2] searched MAUDE for the brand name (da Vinci) and manufacturer (Intuitive Surgical), included reports if they reflected gynecological procedures by description or procedure name, and excluded duplicate reports. Meanwhile, Friedman and colleagues[3] searched for the manufacturer, excluded reports of noninstrument failures or failures caused by an avoidable user error, and

Several regulations, guidelines, and international standards describe how to analyze postmarket data and conduct risk/benefit analyses.

TABLE 1: Clinical Trial Databases

Database	Maintained By	Scope	Description	Link
ClinicalTrials.gov	U.S. National Institutes of Health (NIH)	Worldwide; Drugs, devices, and procedures	Search by any term. Contains publicly and privately supported clinical studies conducted worldwide.	www.clinicaltrials.gov
Postmarketing Surveillance Studies	U.S. FDA	U.S. only; Devices only	Search by applicant name or sort by application date or number. Contains information about the design, tracking, oversight, and review responsibilities for studies mandated under section 522 of the U.S. Federal Food, Drug, and Cosmetic Act.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm
International Clinical Trials Registry Platform (ICTRP)	WHO	Worldwide; Drugs, devices, and procedures	Includes clinical trial registries from more than a dozen countries. Search by any term, including disease state, drug or device, and sponsor.	http://apps.who.int/trialsearch/
EU Clinical Trials Register	European Commission on Public Health	EU and European Economic Area; Drugs and devices	Search by any term, including disease state, drug or device, and sponsor. Splits results into regular and pediatric studies. Gives information on studies with EU Drug Regulating Authorities Clinical Trials (EudraCT) protocol, including title, sponsor, population, medical condition or disease, protocol, and results.	https://www.clinicaltrialsregister.eu/ctr-search/search

The U.S. FDA has the largest, most easily accessible source of postmarket surveillance experience data; however, these databases are potentially limited to the products marketed, sold, and used in the U.S., and are not expected to be comprehensive of the worldwide medical product market.

TABLE 2: Clinical Literature and Clinical Experience Databases

Database	Maintained By	Scope	Description	Link
PubMed	U.S. National Center for Biotechnology Information; U.S. NIH; U.S. National Library of Medicine	Worldwide; Drugs, devices, and procedures	Search clinical literature to obtain abstracts and article information. Some full length articles are available for free in PubMed Central.	www.ncbi.nlm.nih.gov/pubmed
MAUDE	U.S. FDA	U.S. only; Devices only	Search reports from mandatory and voluntary reports by problem, event type, manufacturer, brand name, model, product code, etc.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm
Recalls	U.S. FDA	U.S. only; Devices only	Search by product name, recall number, reason for recall, recalling firm.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm
Warning Letters	U.S. FDA	U.S. only; Drugs and devices	Search by any term or browse by company, issuing office, or subject. Sign up to receive updates automatically.	www.fda.gov/iceci/enforcementactions/warningletters/default.htm
MedSun Medical Product Safety Network	U.S. FDA	U.S. only; Devices only	Clinical sites report events resulting in serious illness, injury, or death as well as "close call" events with potential for harm or other safety concerns. Search by manufacturer, device type or brand, and event or problem description.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/Medsun/searchReport.cfm
Drug Approvals	U.S. FDA	U.S. only; Drugs only	Lists all databases to search for approved drugs, approved inactive ingredients, dissolution methods, clinical investigators, and FDA Adverse Event Reporting System quarterly reports.	www.fda.gov/Drugs/InformationOnDrugs/default.htm

categorized the remaining reports by type of failed part. Although the search steps in each were clear and reproducible, and these two studies analyzed the same product, the analyses differed because one focused on all gynecological procedures and the other focused on which part of the instrument failed, specifically.

Postmarket surveillance analyses should gather and analyze all appropriate clinical trial, literature, and experience or use data from all available databases, as required by regulatory authorities. As defined in MedDev 2.7.1, the clinical evaluation report analyzes three types of clinical data, including clinical trial, clinical literature, and clinical experience data.

Where to Find Clinical Trial Databases

Company-sponsored clinical trial data are often analyzed internally, and should be fully and carefully analyzed as part of the corporate risk management processes and clinical evaluation reports. Databases like ClinicalTrials.gov provide access to details about thousands of clinical trials and additional clinical trial databases are managed by the FDA, World Health Organization (WHO), and the European Commission on Public Health (see Table 1).

To determine if any clinical trials are being conducted using a particular medical device, the ClinicalTrials.gov website, for example, can be searched by product name. Even if the device is a control in a study and not the experimental condition, the search will often detail the dates, protocols, locations, and results of registered clinical trials (if available).

Searching for clinical trials may lead to the discovery of new and unanticipated (potentially off-label) research uses of the device. Or, the searches may suggest answers to specific questions. For example, if an orthopedic device has a risk of accelerated wear, the clinical trial databases may reveal a study in progress to test the device in younger versus older subjects; the results may support or raise cautions about use of the device in younger patients due to the risk of accelerated wear.

Where to Find Clinical Literature and Clinical Experience Databases

Clinical literature about medical products is often found within a publicly available database known as PubMed (www.ncbi.nlm.nih.gov/pubmed). Many other published literature databases exist; however, PubMed is freely available to the public and stores millions of titles and abstracts from the medical literature around the world.

In addition, clinical experience data about medical products are increasingly stored in readily accessible FDA databases. The U.S. FDA has the largest, most easily accessible source of postmarket surveillance experience data; however, these databases are potentially limited to the products marketed, sold, and used in the U.S., and are not expected to be comprehensive of the worldwide medical product market. The FDA resources include databases for adverse events, recalls, and Warning Letters (see Table 2).

The MAUDE database includes adverse events and product problems dating back to 2004. The Medical Device Reporting database collects adverse events and product problems data back to 2002 and feeds into the MAUDE database.

Adverse events databases can provide information to improve the design of the product. For example, searches may reveal an orthopedic device wears out more quickly than anticipated in young, active subjects, and this information may suggest a labeling change to restrict the use of this device to situations in which the benefit (e.g., in older subjects) outweighs the risk (e.g., of repeat surgery to replace a worn out device).

The Warning Letters database publishes FDA correspondence with product manufacturers about quality system failures, mistakes made during manufacturing, and other regulatory violations. The Drug Approvals page lists numerous resources, including where to search for approved drugs, approved drug products with therapeutic equivalence evaluations, drug codes, approved inactive ingredients, postmarket surveillance requirements, dissolution methods, and more.

Finding Clinical Evidence About Similar Competitor Devices in a Product Class

The TPLC, 510(k), *de novo,* and premarket approval (PMA) databases (see Table 3) provide information about many devices. The TPLC database pulls information from the PMA, 510(k), adverse events (MAUDE), and recalls databases to give a big-picture view of the product class, including details on the number of submissions, product problems, and recalls reported for the device class. Evaluating the safety and performance of a class of devices may allow an assessment of the number of recalls or device issues across many equivalent devices to

Postmarket surveillance analyses should gather and analyze all appropriate clinical trial, literature, and experience or use data from all available databases, as required by regulatory authorities.

TABLE 3: Competitor Devices Databases Maintained by the U.S. FDA

Competitor Devices Search		
Database	**Description**	**Link**
TPLC	Search by device name, product code, or regulation number to find pre- and postmarket data about medical devices. Pulls information from PMA, 510(k), adverse event (MAUDE), and recall databases.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/tplc.cfm
Premarket Notification [510(k)]	Search by 510(k) number, applicant name, device name, product code. Contains information of cleared 510(k) applications, including equivalence and indications for use.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
De Novo	Search by *de novo* number, 510(k) number, product code, device name, requester name. Contains information of cleared *de novo* applications.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm
PMA	Search by applicant, trade name, decision date, product code, PMA number. Contains information on approved PMAs.	www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Outside the U.S., fewer databases provide publicly available postmarket surveillance information.

TABLE 4: Additional Databases Outside the U.S.

Database	Maintained By	Scope	Description	Link
Eudamed	European Commission on Public Health	EU only; Drugs, Devices, and IVDs	European Databank on Medical Devices: provides access for EU Member State's Competent Authorities to information on manufacturers, devices, adverse events, clinical investigations, and adherence to requirements of CE Mark registration.	http://ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm
NCAR	European Commission on Public Health	EU only; Drugs, Devices, and IVDs	National Competent Authority Report: generated by each EU country's national Competent Authority, these reports on adverse events of medical devices or *in vitro* diagnostics only list the report number and country of origin with no further details.	http://ec.europa.eu/health/medical-devices/documents/vigilance-reports/index_en.htm
MedEffect Canada	Health Canada	Canada only; Drugs and Devices	Search by any term. Provides information on adverse reactions, advisories, warnings, recalls, and side effects.	www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
SwissMedic	Swiss Agency for Therapeutic Products	Switzerland only; Devices only	Search for recalls and issued advisories using any term.	https://www.swissmedic.ch/rueckrufe_medizinprodukte/suche/index.html?lang=en
DAEN	Australian Therapeutic Goods Association (TGA)	Australia only; Drugs and Devices	Database of Adverse Event Notification: search by product name, date range.	https://www.tga.gov.au/database-adverse-event-notifications-daen

estimate if the recorded information is typical of the entire class of devices.

The 510(k) database provides information on premarket notifications submitted to the FDA. These devices are cleared based on substantial equivalence to existing devices. If a device was denied clearance through a 510(k) application, and is not a high-risk class III device, this device may have gone down the *de novo* path, and would be listed in the *de novo* database. The *de novo* database is home to low-risk devices without an equivalent device on the market, whereas the PMA database is for high-risk devices which must be approved for the market by the FDA.

Consider the previous example of an orthopedic device wearing out quickly in a young patient population, and note the 510(k), *de novo,* or PMA databases can provide information on other companies marketing similar orthopedic devices. This information can then be used to search the adverse event (MAUDE), recalls, and other databases to see if competitor devices reported similar accelerated wear issues. The TPLC database will also give an overview of all devices in the orthopedic device class, including the most common adverse events and number of recalls. This information can inform whether the orthopedic device has a design flaw particular to a single device or the entire device class.

Finding Information Outside the U.S.

Outside the U.S., fewer databases provide publicly available postmarket surveillance information (see Table 4). These include the two international clinical trial databases mentioned earlier: the International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register.

In addition, recalls issued by the Swiss Agency for Therapeutic Products can be searched on the SwissMedic database, and Health Canada allows public searches of advisories, warnings, recalls, adverse reactions, and side effects on its MedEffect Canada site; however, this database is not as easy to search, and has far less data compared to the U.S. databases.

The European Databank on Medical Devices (Eudamed) and the National Competent Authority Report (NCAR) collect information from the medical device community similar to the U.S. FDA; however, the EU does not provide public access to its safety databases. These EU databases allow countries within the EU to disseminate important information to each other; however, they have no publicly available searching capabilities on their websites. NCAR issues annual reports detailing how many countries had device problems reported to NCAR, and the names of the countries are published, but the device problems are not specified.

Conclusions

The full and complete analysis of postmarket surveillance clinical data is critical to understanding the performance and safety of a medical product. Publicly available databases will often identify events not reported to the manufacturer and worthy of inclusion in postmarket surveillance reports. These reports should also include data about substantially equivalent competitor products.

Including the appropriate information in a postmarket surveillance report or clinical risk/benefit analysis improves risk monitoring by potentially identifying new risks to be added to the risk management activities. The Notified Body will look for postmarket surveillance data as required by the regulations, guidelines, and standards. Using free, publicly available databases for postmarket surveillance may be especially helpful to capture information about infrequent events, long-term-use events, or patterns of adverse events indicating a problem in product design.

Although these free data are useful, avoiding the known limitations of these databases is critical. For example, MAUDE data are not intended for evaluating or comparing rates of adverse events across similar devices; only general descriptive information should be drawn from these data.[4] The main limitation of MAUDE is selective reporting of adverse events. Mahomed and colleagues[5] indicated mandatory device reporting systems (such as MAUDE) underreported adverse events, and Kramer and colleagues found the FDA recalls system poorly measured the actual performance of medical devices given the "complexities in recognizing postmarket events and translating these into FDA action."[6]

Using free online databases can expand postmarket surveillance activities and can help the researcher identify previously unknown risks, benefits, or design issues with a product. This information must then cycle back into risk management processes, clinical evaluation reports,[7] and clinical risk/benefit analyses to satisfy regulatory requirements.

Overall, the current, free online databases can augment, but not replace, a company's internal surveillance of medical device products.

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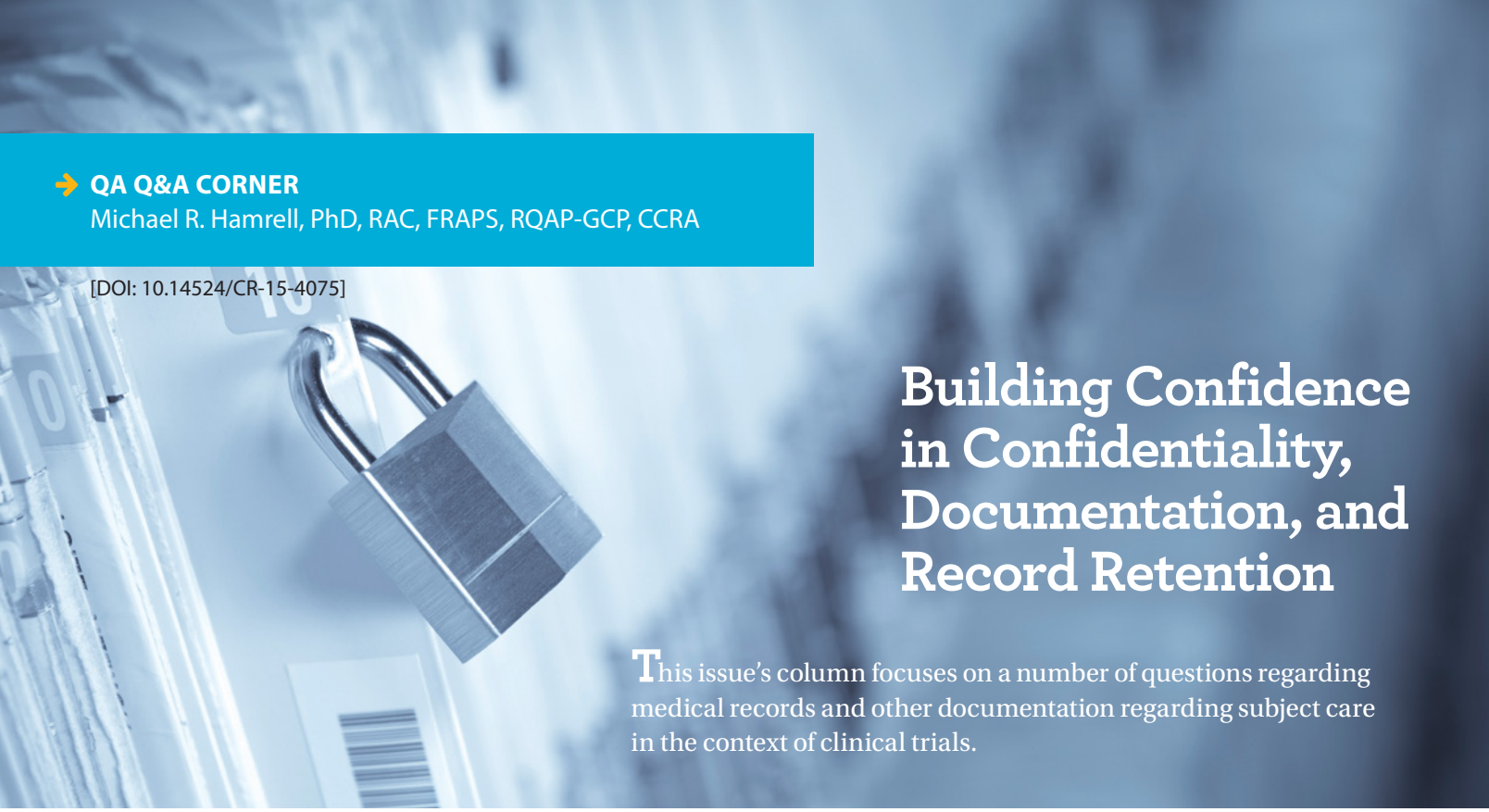

Building Confidence in Confidentiality, Documentation, and Record Retention

This issue's column focuses on a number of questions regarding medical records and other documentation regarding subject care in the context of clinical trials.

Q: There has been an ongoing discussion regarding the confidentiality of subjects' medical records and case report forms (CRFs). As the industry transitions to electronic medical record (EMR) systems, this seems to be more and more important. How is confidentiality viewed and balanced against the need by clinical research associates (CRAs) to review medical records?

A: It is perfectly acceptable to place study information into a subject's EMR. In fact, it is recommended. Specifically, the guidance document on investigator responsibilities (see www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf) even recommends that the clinical investigator directly inform the subject's personal physician if the subject agrees to participate in a clinical trial.

The purpose for including study information in the EMR is to allow others who would need to treat the individual and who would review the EMR—on either a routine or emergency basis—to be aware of study treatments and/or any adverse events that were observed to better inform their diagnosis and treatment. This would include CRAs from another study who might at some point review the same record, and thus become aware that a subject was on another study from a competitor; this may be critical information in determining eligibility.

There should be no issue of confidentiality in placing study information in the EMR, since the EMR needs to be maintained to at least the same level of confidentiality as study records.

Q: In its *Code of Federal Regulations* (CFR), U.S. Food and Drug Administration (FDA) drug regulations at 312.62(b) and comparable regulations for medical devices at 812.140(a)(3), require clinical investigators to prepare and maintain "adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation." What characteristics make a source document/chart "adequate"?

A: In an informal response to this question, the FDA has stated that, "what constitutes an 'adequate source document/chart' is a bit of a subjective judgment." There is no clear definition that would fit all of the possible scenarios that arise in the clinical trial environment. This is why the strict regulatory language uses the term "adequate" when discussing the records the clinical investigator is to maintain.

The term "adequate" in this context implies that records are suitable for their intended use, and they can be used to verify the quality and integrity of information that is collected and ultimately submitted to FDA. The records should be **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, and **A**ccurate (to pass the ALCOA test). The extent to which a record possesses all or none of these quality elements places it on a quality scale, while the integrity of the information is determined by establishing the extent to which information

is consistent, credible, and corroborated. Data quality and integrity, taken together, establish the degree of confidence that FDA (and the public) may have in relying on the information for regulatory decision making.

Do you have a GCP question or an issue that has come up at your site or company? If you are not sure of how to proceed, please send an e-mail to: gcp@moriahconsultants.com and I will answer it in an upcoming column.

Q: FDA CFRs require clinical investigators to retain study-related records and reports for specific periods (§312.62(c) and §812.140(d)). However the regulations say nothing about standards for the storage and protection of these records. Is it expected that a site would use fireproof or locked cabinets (or any related standards) to maintain the physical security of study records?

A: The regulations are silent on the topic of physical security for study-related records and information. While there is plenty of guidance on the need to protect subjects' confidentiality through the Health Insurance Portability and Accountability Act, there is little guidance on physical measures to maintain record confidentiality.

Although it is important to preserve paper records, there is no specific requirement in the regulations for fireproof or locked cabinets to store clinical trial records. It may be useful to consult with your institutional review board or with your institution's research office for any recommendations on this topic.

In addition, as more of a study's research records and documentation is now maintained and stored electronically (eCRFs and electronic trial master file documents), the need for a locked cabinet is less necessary or relevant. In this case, it is also necessary to consider adequate computer security regarding the storage of study records.

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BIOVISUALIZATION:
Enhancing Clinical Data Mining

PEER REVIEWED | Hermioni Zouridis, PhD

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Even as many clinicians struggle to give up their pen-and-paper charts and spreadsheets, some innovators are already shifting healthcare information technology into a new paradigm. Researchers, players in the greater pharmaceutical industry, and other stakeholders are analyzing huge amounts of aggregated information—big data—to elucidate patterns that remained hidden under old data models. Blending biostatistics, bioinformatics, computer programming, and operational research, big data are expected to transform the process of clinical decision making. Much of these data will come from clinical trials.

Accurate and timely data management begins with detailed and proven processes. By combining these processes with state-of-the-art data management platforms, researchers can ensure the delivery of clean data in accord with exact specifications. The ever-increasing volume of clinical and laboratory data represents a substantial resource that can provide a foundation for the improved understanding of disease presentation, response to therapy, and healthcare delivery processes.

Data mining supports these goals by discovering, unraveling, and, sometimes, anticipating similarities and relationships between data elements in large datasets. Currently, medical data poses several characteristics that make the application of these techniques difficult, although there have been notable medical data-mining successes. Future developments in integrated medical data repositories, standardized data representation, and guidelines for the appropriate research use of clinical data will decrease the barriers to mining projects.

DATA VISUALIZATION

Large, complex datasets are generated throughout a clinical trial. Biovisualization platforms are tools that enable effective data mining and ease of data interpretation. Understanding the underlying trends within data is vital to making critical decisions and accelerating time to market. However, data analysis can be challenging, time-consuming, and tedious.

Increasingly, in-house biostatisticians—especially within large pharmaceutical companies—are being asked to undertake complicated and time-consuming exploratory analyses or to look at data in "different ways." Researchers want to know how to partition the demographics; they want to think differently about the data so they can stratify their populations and, perhaps, formulate a hypothesis for what might be a potential biomarker for a new drug.

Another key driver behind developing these biovisualization platforms was the need to understand clinical data in real time (during the trial), which allows sponsors and moderators to make informed decisions more quickly and efficiently. During a clinical trial, vast quantities of numerical data are generated. Traditionally, that information was deposited into a huge collection of vast spreadsheets and manually assessed and analyzed. Literally, researchers and scientists were left to stare at long columns of numbers and try to make sense of the trends within. Now, technology provides a better way.

SPOTTING THE OUTLIER

The rapidly increasing amount of data in biological research, experiments, and clinical trials calls for effective data analysis techniques. Visual analytics techniques have proven to be an effective way to analyze biological data, enabling researchers and trial sponsors to combine the strength of automatic methods with the expert knowledge of the analyst.

So, the benefit of having a biovisualization tool is to go beyond the numbers and look at the visual representations that can be created with the data, which allows reviewers to find, for example, any individuals within a subject group demonstrating out-of-specification results or outlier measurements that might require further investigation or intervention. They could also identify any unanticipated trends within a certain population.

With visual data analytics techniques, researchers can take advantage of the raw feed data, explore it further, and get a deeper understanding of that information to motivate novel hypotheses—all while monitoring the data to make sure that nothing abnormal is happening.

THE TOOLS AVAILABLE

Many providers have recently introduced visual data analytics platforms and found that a one-size-fits-all approach to biovisualization has its limitations. For example, bioinformatics experts may find a preprogrammed platform too restrictive, but, for a biologist or scientist at the bench, it can be too complicated. Consequently, when additional bioinformatic-type analysis must be performed, scientists often bypass visual data analytics platforms and go directly to their in-house resource.

Customizability is an important aspect of the tool: The data that the researchers are compiling are unique, and they should have access to a platform that's flexible enough to exploit these data.

Although data mining has been around for some time, the scale of the datasets has become enormous. Intuitive, highly interactive computational tools that perform analyses and visualize unknown trends, patterns, and outliers offer a way to identify buried opportunities and risks and provide a competitive advantage. These tools accelerate the decision-making process and facilitate the identification of noncompliant results.

FUNCTIONALITY

Biovisualization tools can help researchers go beyond a simple pie or bar chart to delve further into the data. Increasingly, researchers are using these platforms for two key reasons: to spot potential problems before they become major issues (from data quality or medical monitoring perspectives, for example); or to answer scientific research questions regarding biomarker evaluation or integrating study-specific information, such as dose cohort or toxicity metrics. Laboratory measurements of components in samples (i.e., analytes) from individual subjects can be displayed to review data from and provide answers to these questions.

Furthermore, demand has been rising for more modular, customizable biovisualization tools, such

Researchers, players in the greater pharmaceutical industry, and other stakeholders are analyzing huge amounts of aggregated information—big data—to elucidate patterns that remained hidden under old data models.

FIGURE 1: A PCA Plot with the Data Points Shaded by Visit

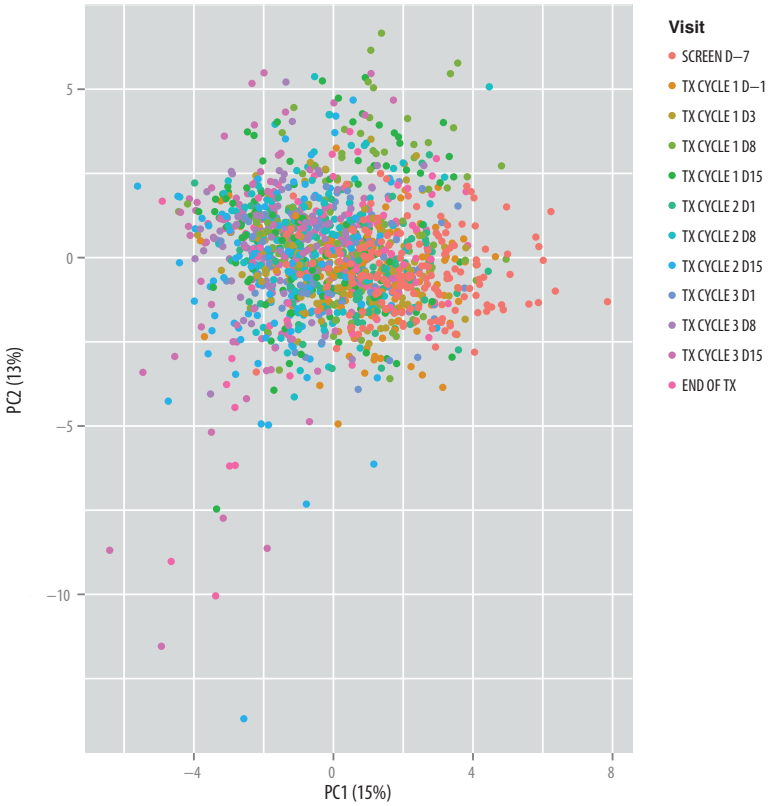
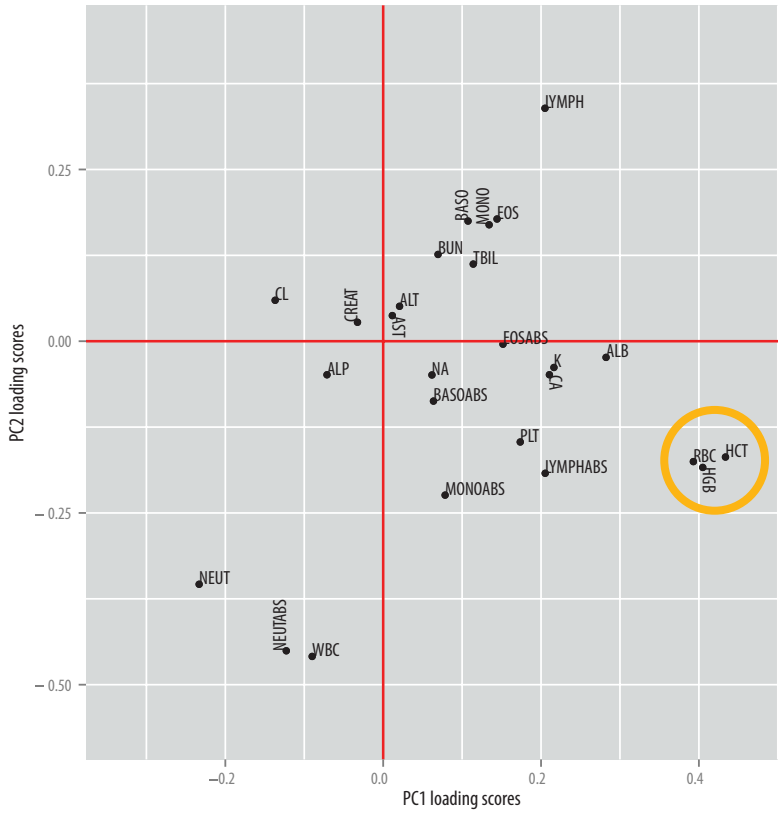


FIGURE 2: Hemoglobin (HGB), Red Blood Cell (RBC), and Hematocrit (HCT) Measurements Have Large Loading Scores and Co-Localize on the Loading Plot (Circled in Yellow), Strongly Influencing PCs and Showing Similar Behavior



as those that can be adapted so research personnel can access a very specific figure in a more meaningful format. As described in the following sections, depending on the analysis required, there are different options to choose from.

PRINCIPAL COMPONENT ANALYSIS (PCA)

The goal of the PCA technique is to use all the analyte measurements to find, if possible, hidden structure in the data by minimizing redundancy and maximizing signal strength. Variables (analyte measurements) are transformed into new variables called principal components (PCs).

Each PC is a linear combination of analyte measurements weighted by each analyte's loading score. The first principal component (PC1) accounts for the highest percentage of variance in the data; the second principal component (PC2) represents the second-highest percentage of variance, and so on.

PCA plots (PC1 versus PC2) allow users to determine study factors (e.g., visit, investigator site, dose cohort, age group) linked to variability in analyte measurements, and can often reveal unseen patterns.

Figure 1 is an example of a PCA plot with the data points shaded by visit. At a glance, variability in study measurements linked to visit is expected by observing the clustering of the points along PC1. The far right section of the plot is populated by mostly orange and yellow points, which correspond to visits at the beginning of the study. The center section is populated mostly by green and light blue points, which correspond to visits in the middle of the study. The far left section is populated mostly by purple and dark blue points, which correspond to visits at the end of the study.

Since analytes' respective loading scores weight PCs (see Figure 2 for an example), they can be checked to better understand each analyte's contribution to PCs, remembering the following points:

- The greater the loading score magnitude (positive or negative) for a particular PC, the more that analyte's measurements influence that PC.
- The closer to zero the loading score is, the less that analyte's measurements influence that PC.
- Analytes that co-localize on the loading plot are expected to exhibit similar behavior.

Inspecting Figure 2 reveals that hemoglobin (HGB), red blood cells (RBC), and hematocrit (HCT) have large PC1 loading scores (outlined in yellow), indicating these analytes strongly influence PC1. Since data variability linked to visit is expected from the clustering pattern along PC1 (Figure 1), these analytes' measurements are anticipated to

vary markedly by visit. Also, these analytes are expected to exhibit similar measurement patterns, as they co-localize on the loading plot (Figure 2). Therefore, we would expect that HGB, RBC, and HCT will all vary substantially by visit and in a similar way.

Taken together, PCA (Figure 1) and loading (Figure 2) plots empower the user to rapidly identify study factors and analytes of potential clinical significance that may warrant more detailed investigation.

One way to examine analyte measurements is with boxplots, either for the whole population (see Figure 3) or separated by demographic (e.g., investigator site, dose cohort, age group). Each box represents the middle 50% of the data, with the horizontal line within it representing the median. Hence, the boxplots in Figure 3 provide both trending and distribution information by visit.

The RBC measurements in Figure 3 exhibit a marked downward trend over time, with the observed visit-linked variability consistent with the observations in the PCA (Figure 1) and loading (Figure 2) plots. The horizontal red lines represent the upper and lower reference limits, providing context to the results.

An example of a PCA-based workflow involves clinical personnel first consulting PCA plots to determine factors associated with variability in the data, then inspecting loading plots to identify analytes of interest, and last checking relevant boxplots to learn about analyte trends and distributions. Research scientists may conduct this workflow centered on dose cohort or disease subtype. Such exploratory analysis may reveal biomarkers underpinning differences between these groups, or confirm expected results.

Furthermore, medical monitors could rapidly identify demographics and analytes with potentially alarming trends. Project managers may be interested assessing investigator site performance. This workflow could help identify sites associated with distinct data patterns that beg for follow-up investigation (e.g., are differentiating factors linked to sample mishandling?).

HEATMAP

As shown by Figure 4, the purpose of a heatmap is to identify studywide patterns in analyte measurements over time, whereby the color of each cell is proportionate to the study population's median analyte measurement (0 = white, 1 = deep blue) for a particular visit after scaling. The HCT, HGB, and RBC measurements (outlined in yellow) are relatively high at the beginning of the study and drop off with time.

FIGURE 3: A Boxplot Displaying the RBC Measurements of a Study Population Regarding Visit, Allowing the User to Observe Trends with Ease

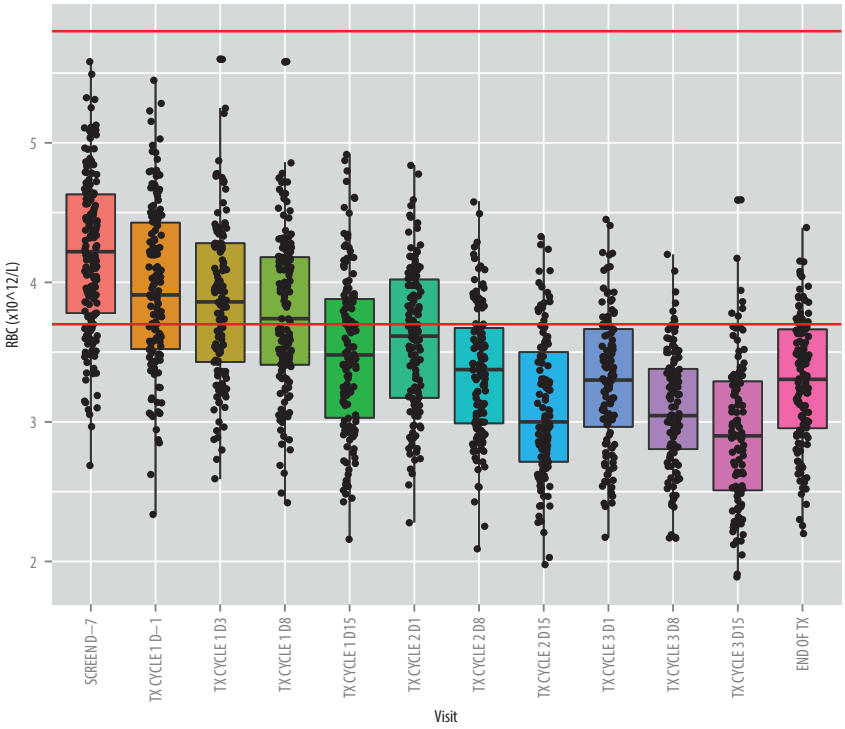


FIGURE 4: Heatmap of Visit-Specific Median Analyte Measurements After Scaling (Whole Study Population)

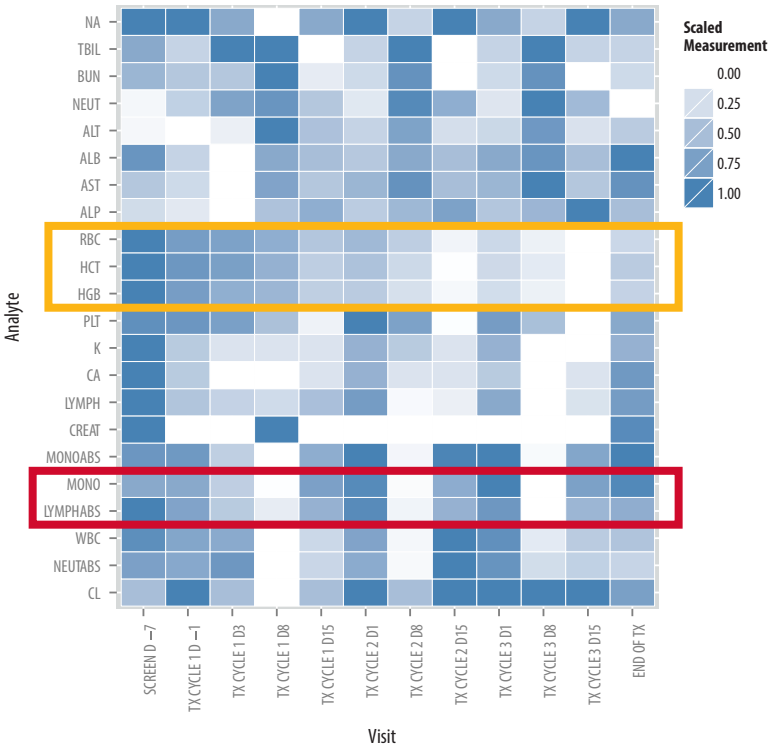
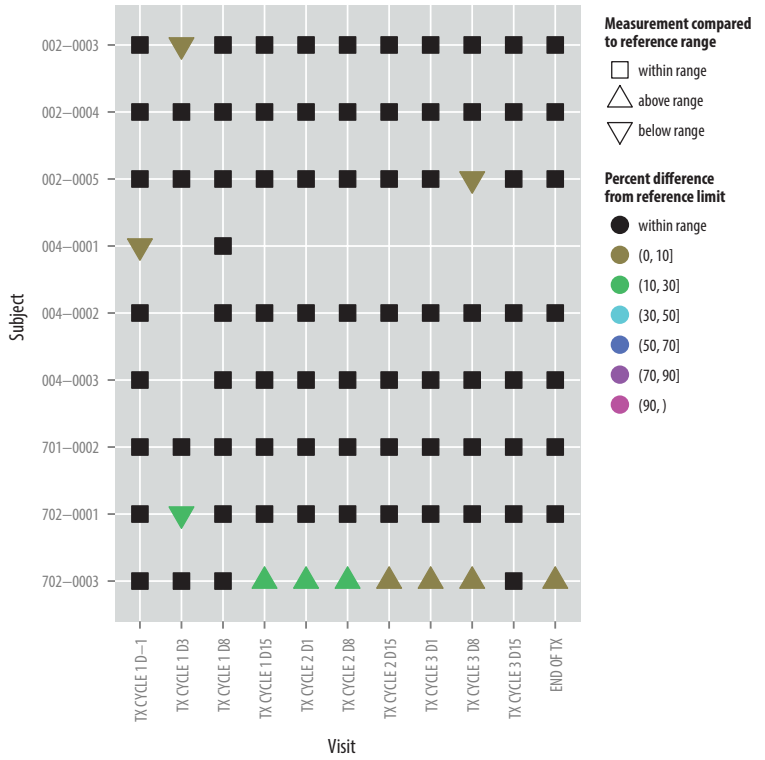


FIGURE 5a: A Reference Range Comparison of ALB for Male Subjects



Biovisualization platforms and services are particularly useful for large and, perhaps more immediately, smaller pharmaceutical companies that might not have the staff, time, or resources to undertake the extent of data analysis required to safeguard the ongoing process of their clinical trial.

Other measurements, such as monocytes (MONO) and absolute lymphocytes (LYMPHABS) (outlined in red), tend to be oscillatory with time, because they start out at an intermediate level and then spike downward, return to the intermediate level and then spike downward again, etc.

Heatmaps are useful to research scientists and medical monitors for rapidly confirming expected trends (e.g., analyte responses to drug treatment) or discovering unexpected trends. Heatmaps could also complement the workflow described in the previous section.

REFERENCE RANGE COMPARISONS

An area of concern in clinical trials is how analyte readings compare to acceptable reference ranges. The reference range figures that follow allow users to assess comparisons in three ways: first as a summary for a subset of the whole population (Figure 5a); then, as a subject profile (Figure 5b); and, finally, in a single-analyte-single-subject manner (Figure 5c).

Figure 5a is an example of a summary for a specific analyte (albumin (ALB)) and demographic (males). Rows and columns represent subject IDs and visits, respectively. Each entry conveys information based on the colors and shapes described in the legend. Black squares mean that corresponding measurements are within the analyte's reference limits, while upward and downward facing triangles indicate measurements above and below the upper and lower reference limits, respectively. The colors of the triangles represent the percent differences between the measurements and the breached reference limits.

Figure 5b is an example of a summary for a specific subject. Rows represent analytes and columns visits, with entries conveying the same information as Figure 5a.

Figure 5c is a plot of measurements for a single analyte from a specific subject. The horizontal black lines represent the upper and lower reference limits, providing context to the results.

Such figures enable medical monitors to rapidly assess demographics, subjects, or analytes with potentially alarming trends. For example, in Figure 5a, subject 702-0003 jumps out because the corresponding measurements are consistently above the established reference interval. This subject can be further explored by examining a subject-specific profile (Figure 5b), noting that the lymphocyte (LYMPH) and platelet (PLT) results may seem interesting because they are consistently below their respective reference intervals. In either case, further information can be extracted from the data by examining the individual's records in more detailed plots like Figure 5c.

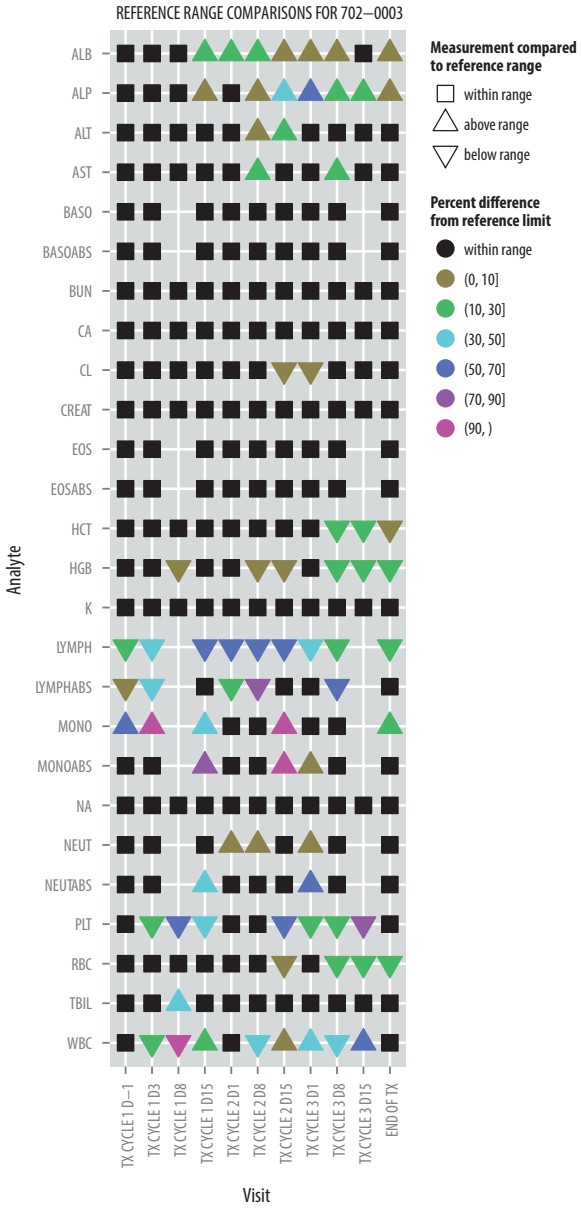
BENEFITS

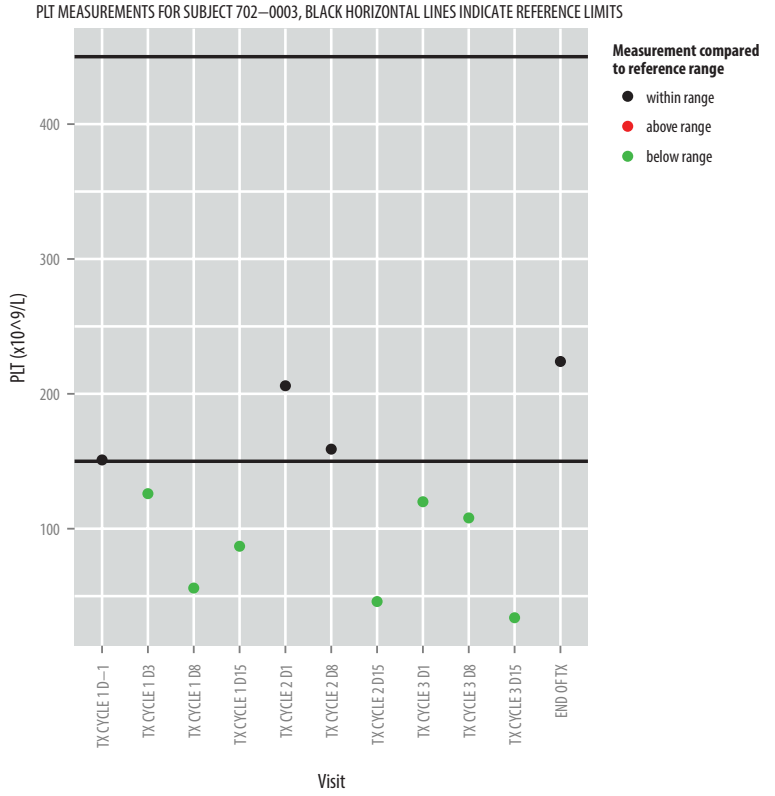
Biovisualization platforms and services are particularly useful for large and, perhaps more immediately, smaller pharmaceutical companies that might not have the staff, time, or resources to undertake the extent of data analysis required to safeguard the ongoing process of their clinical trial.

Irrespective of the labor and costs, small, medium, and large product developers—perhaps lacking access to teams of in-house biostatisticians—unfortunately often resort to spending more time than necessary to sift through data and then report the results of the trial, without analyzing the trends and uncovering hidden but valuable information. Often, a biovisualization tool is a viable way to free up in-house staff to work on in-house development, research, and infrastructure projects rather than having them sift through data.

The purpose of biovisualization platforms is not to perform a large amount of rigorous statistical analysis, but to offer different quantitative biovisualization techniques to explore the data and formulate hypotheses that can then be discussed and used to initiate further analysis; the purpose

FIGURE 5b AND c: Reference Range Comparisons for an Individual Subject





"The commonality between science and art is in trying to see profoundly — to develop strategies of seeing and showing."

– Edward Tufte

is to have a conversation with the data to better understand them, which makes the decision-making process more efficient. A company might wish to terminate a trial, depending on the results it is getting, or it may be inspired to further investigate a drug-specific biomarker.

The importance of data management in clinical trials cannot be overstated. To cite a recent example, a pharmaceutical company found that trial subjects were experiencing adverse side effects; however, the alarm was not set off by the medical monitors, but by the data management team, emphasizing the growing role that advanced data analysis will play in making rapid, mission-critical decisions and bringing drugs to market.

Biovisualization tools and their attendant interpretative services provide scientists and medical monitors a way to see their data more clearly—literally. The art of bringing data to life through simple visual displays may lead to profound observations revealed more quickly, ultimately adding speed and efficiency to the drug development process.

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Martin Robinson, PhD

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MEASURING THE IMPACT OF RISK-BASED TRAINING

Building on my previous column about risk-based training, the topic of this issue's piece is how to measure the impact of a training or learning intervention. One of the most cost-effective ways of identifying training needs and then meeting them is to use a risk-based approach. In other words, where are the high-risk areas of noncompliance, and what impact ultimately do they have on the protection of patients and data integrity?

Using a risk-based approach to training allows a much more targeted approach to be taken, and increases the chances of identifying the right metrics to measure while taking into account some of the other noteworthy factors.

Measuring the direct impact of training is often a challenge. Return on investment (ROI) is commonly used to try and gauge the financial benefits that investing in training might bring.

From an organizational and business point of view, this makes sense. No organization wants to spend money without gaining some kind of benefit. However it is not always possible to ascertain exactly what an organization has gained financially as a result of training.

In the context of clinical research—where there are ethical as well as financial issues at stake—it can be useful to take a wider view on what "return" means, and consider it in terms of benefits to the clinical trial patients, individual members of the workforce, and the organization as a whole.

Leverage Risk Analysis

As I described in the previous issue, by using a risk management approach, the major threats can be identified and a plan put in place for preventing or mitigating them. These threats can be tracked in terms of whether they manifest themselves entirely, partially, or not at all. An analysis can be made about the impact of training on threat reduction.

For instance, if risk-based training was conducted on specific areas of a highly complex protocol, a suitable measure of effectiveness could be an analysis of protocol deviations, particularly those affecting patient safety and data integrity. Further training could be conducted (if relevant) if protocol deviations were being caused by previously unidentified factors.

Use Key Performance Indicators

Key performance indicators (KPIs) are quantifiable measurements that reflect the critical success factors of an organization, department, or team. KPIs should be quantifiable and related to core activities that are critical for success. Analysis of KPIs, pre- and post-training, can determine what effect training can have in objective and measurable terms.

KPIs can be set at the organizational, departmental, or team level. Some examples might include number of regulatory authority inspection serious findings, number of noncompliance incidents requiring corrective and preventive actions (CAPAs), and, for investigator sites, actual numbers of eligible patients recruited versus those planned.

When Should You Use Financial Metrics?

In terms of the effect of risk-based training in reducing numbers of regulatory authority findings and CAPAs, a financial figure can be ascribed to this by calculating the cost of wages (number of hours in effort) in implementing the actions.

Naturally there are some direct financial benefits from certain types of training. For example, a contract research organization might be able to demonstrate an increase in volume of repeat business through improved customer satisfaction after introducing a company-wide training program on providing excellent client service. How this increase in volume has been achieved may be due to a number of factors; however, the effect of the training can be evaluated by asking customers specific questions about the degree to which their requests, queries, or complaints were satisfactorily handled.

Responses to a survey conducted before the training was carried out may have revealed some initial problem areas. Once the training has been implemented, and after a suitable time interval, a post-program survey asking the same questions will reveal if any improvement has been gained.

Many organizations consider staff turnover a threat to business continuity and performance excellence. Not only that, but replacing staff is a costly exercise. PricewaterhouseCoopers conducted research showing that hiring a new person to replace an existing employee who is performing well can cost the firm almost that person's annual salary.[1] A separate survey[2] revealed that the number one reason for people leaving their job was that they felt that they were being poorly managed.

If staff surveys on an individual organization revealed the same pattern, it follows that one method of assessing the ROI in management training could be to examine staff turnover numbers, with a financial score being assigned to the cost of hiring new staff to replace those who have left.

Can You Measure Training Impact?

There have been numerous scholarly articles written on measuring the impact of training. One well-known framework is that of Kirkpatrick,[3] who describes a four-level model starting with the reaction of the individual learner (level 1) up to level 4, which is the effect on the business or environment resulting from the improved performance of the trainee.

However, one of the challenges in measuring the direct effect of training is the number of other factors that can affect individual and collective staff performance. These include the systems and processes that are in place (e.g., standard operating procedures), the way the organization is structured (e.g., multilayered/hierarchical or flat), and the style and capability of management.

Remember…

Using a risk-based approach to training allows a much more targeted approach to be taken, and increases the chances of identifying the right metrics to measure while taking into account some of the other noteworthy factors.

The ultimate measure of success of risk-based training is the effect it has in protecting the wellbeing and rights of clinical trial subjects, which makes good business sense, too.

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OPINION

Is There a Prescription for Finding Top Talent in the Life Sciences Market?

PEER REVIEWED | Kevin D. Duffy, MBA

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Strategic resourcing models employed within the biopharmaceutical sector have been a hot topic lately—and for good reason. In the last decade, markets for life sciences products and services have increased exponentially, which means having the right talent in place is essential for any company with plans to protect and grow its share of the market.

Further, while business operations have expanded to serve these markets, there's no question that the size and availability of a qualified workforce is a critical factor in industry growth. For a look at how a talent shortage is impacting industry, see the Interim Executive Director's Message on page 8.

Gaining a keen understanding of the talent a company has and hopes to attract in the future is imperative. In fact, it's the foundation for creating effective strategies in workforce planning, talent analytics, and talent supply chain management.

Do You "Get" Your Own Workforce?

The most visible of these strategies has been the utilization of a "functional service provider" or "functional service provision" model to augment and/or supplement existing in-house staff to meet the variable resource needs of a clinical operations team. This popular model was born on the heels of the various strategic partnering arrangements that have evolved over time in this space, and have become a standard offering within the contract research organization community and global talent acquisition firms.

As we've seen research and development portfolios expand and transform with more specialized drug compounds, targeted therapies, and personalized medicine, it's become clear the life sciences industry's short- and long-term strategies to hire high-quality talent must evolve as well. Ultimately, those strategies need to be crafted to enable scientists and clinical research professionals to focus on speed to market, innovation, and rapid decision-making to address the changing needs of the dynamic drug development sector.

It's also clear that the talent supply chain must become more flexible and adaptive to remain competitive in the marketplace. Just as a supply chain of raw goods and materials is managed in manufacturing, access to skill-specific talent can be effectively procured and managed using a talent supply chain in which a talent advisor provides clients just-in-time talent that ranges from temporary workers, independent contractors, service providers, alumni/retirees, and/or full-time employees.

Biopharmaceutical and medical device companies must make sure they're tuned in to the needs of this talent pool, and have a better understanding of its members' personal goals and objectives.

How to Attract Top Talent

So what is the talent pool looking for? Certainly, traditional things like the desire for growth opportunities, job satisfaction, and competitive compensation still matter. However, there's also a strong desire for daily intellectual stimulus and more collaborative work environments.

Further, a firm's overall reputation and corporate culture also are gaining in importance for the pool.

Five areas identified in the most recent Kelly Global Workforce Index report,[1] published in March, 2015, reveal actionable conclusions that can inform and improve corporate talent recruitment strategies:

1. **The candidate application and onboarding experience.** Those in the talent pool want regular communication about application status, and after hiring, they expect more structure in learning about the company's culture and business model; such practices will increase successful outcomes for the candidate and worker, respectively.

2. **The channels for engaging active and passive job seekers.** Employers must meet the candidate's communication preferences and utilize these engagement vehicles, whether via social media, online talent communities, professional networks, or other means to successfully recruit critical talent.

3. **Career development.** Most workers would rather focus on acquiring new skills, not on climbing the company's ladder. Guiding workers with their career development can help retention and lead to better performance.

4. **Worker preferences.** Companies are now forced to offer more incentives to attract talent, including nontraditional work styles, environments, and arrangements, as the demand for talent becomes more competitive.

5. **Employer performance.** The concept of an "employer talent quotient" measures a company's performance in offering its talent good work/life balance, exposing them to the latest technology, practicing diversity, adhering to environmental practices, and providing meaningful work.

More than any other characteristic spotlighted in the workforce report, life sciences workers prefer to collaborate with their peers. In fact, nearly seven in 10 (68%) feel the ideal workplace provides a highly collaborative environment, which is significantly more than the global average (57%).

Get Them…And Keep Them

Even before the hire, employers should already have a strong onboarding program in place. The majority of life sciences workers undergo some form of onboarding once hired, and this experience can be leveraged to foster a positive impression of the company. This value-added practice is often a big factor for employees mulling whether to stay or go during the first 90 days.

Of particular interest, in the aforementioned workforce report, more than half (56%) of life sciences employers had a planned onboarding approach for assimilating them into the organization, on par with the global average (55%).

Significantly more life sciences employers in the Asia-Pacific (63%) and the Americas regions (59%) had a planned onboarding approach for assimilating workers into their organizations, compared to those in Europe-Middle East-Africa (52%). Further, 81% of life sciences workers feel that their experience during the first 90 days of employment positively affected their impression of the company, comparable to the global average (80%).

Close to half (47%) of life sciences workers feel that their experience during the first 90 days of employment definitely made a favorable impression, on par with the global average of 45%. Lastly, significantly more workers in the Americas (53%) compared to their regional counterparts (41% each for Asia-Pacific and Europe-Middle East-Africa) feel this experience *definitely* made a favorable impression.

Ingredients for an Attractive Workplace

Employers who invest in integrating a myriad of workplace approaches may have the most success in attracting and retaining talent. There is a strong representation of life sciences workers who prefer a highly collaborative environment, but it is clear that flexible work schedules and the opportunity to utilize cutting-edge technology are also ideal work environment features.

More than any other characteristic spotlighted in the workforce report, life sciences workers prefer to collaborate with their peers. In fact, nearly seven in 10 (68%) feel the ideal workplace provides a highly collaborative environment, which is significantly more than the global average (57%). More than half of life sciences workers (55%) feel the ideal workplace provides flexible work arrangements, which is on par with the global average (54%).

Far more life sciences workers in the Americas (61%) and Asia-Pacific (60%) feel that a flexible work arrangement is an ideal workplace feature, compared to those in Europe-Middle East-Africa (46%). Further, 59% of members of the "Generation X" and "Baby Boomer" eras identified a flexible work arrangement as a compelling feature.

Significantly more life sciences workers than global workers note that exposure to latest technologies and the culture of innovation and creativity are desired work environment features (51% versus 44%; and 48% versus 39%, respectively). A greater incidence of life sciences workers in the Americas (56%) view exposure to latest technologies as an ideal feature, compared to those in Asia-Pacific (48%) and Europe-Middle East-Africa (44%).

Other work environment features that are significantly different between life sciences workers and the global average include:

- Life sciences workers feel that a matrixed organization structure is an ideal work feature; significantly more so than the global average (33% versus 29%).
- However, significantly fewer life sciences workers compared to the global average feel that traditional work arrangements (24% versus 32%) and a competitive environment in which the rewards and risks are high (19% versus 21%) are ideal work features.

Reading the Signs

So what can employers do to be proactive in planning to meet staffing challenges head-on and maximize their employee satisfaction and retention?

In many cases, employers should turn to the experts. The pharmaceutical, biotechnology, and medical device industries in the United States have historically failed to invest sufficient resources in building internal teams and developing long-term succession plans for their workforces. However, smart, forward-thinking, and established firms are increasingly partnering with consultative workforce organizations to fill their talent gaps. Workforce solutions companies can offer valuable assistance in locating contractors with niche skills, as well as streamlining and speeding up the hiring process to fill permanent positions quickly.

In the end, biopharmaceutical companies need to take a holistic approach to their talent supply chain and human capital strategy to identify the right talent, at the right time, in the right place. It will prove to be a smart, strategic investment for exploring the scientific frontiers of drug development that will pay big dividends.

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[DOI: 10.14524/CR-15-4079]

A CLOSER LOOK: California Protection of Human Subjects in Medical Experimentation Act—**Federalism and Research Law**

The tangled regulatory structure for clinical research in the U.S. is a result of the grand power-sharing compromise that the founding fathers proposed when they drafted the Constitution.

For 200 years, both the federal government and the states have promulgated laws to promote health and provide for the general welfare of the people. This has created a highly fragmented system—one in which you have physicians licensed by the state and bearing credentials granted by peers to practice in hospitals regulated by overlapping state and federal government laws.[1] This tangled regulatory structure is a result of the grand power-sharing compromise that the founding fathers proposed when they drafted the Constitution for the United States.[2]

Individual state laws complement federal clinical research laws, and govern everything from informed consent[3] to property rights[4] for research subjects enrolled in clinical trials in the 50 states.

Prior to the passage of the Pure Food and Drug Act of 1906, there was a patchwork of individual state laws and no meaningful regulation of the interstate commerce of foods or drugs.[5] After its passage and that of the larger Federal Food, Drug, and Cosmetics Act of 1938, these laws preempted conflicting state laws. However, individual states are still permitted to pass laws that complement and do not conflict with federal laws.

Federalism describes the "legal relationship and distribution of power between the national and regional governments within a federal system of government."[6] In *Federalist No. 45,* the "Father of the Constitution" James Madison described the dual sovereignty relationship between the states and the proposed federal government:

> The powers delegated by the proposed Constitution to the federal government are few and defined. Those which are to remain in the State governments are numerous and indefinite. The former will be exercised principally on external objects, as war, peace, negotiation, and foreign commerce; with which last the power of taxation will, for the most part, be connected. The powers reserved to the several States will extend to all the objects which, in the ordinary course of affairs, concern the lives, liberties, and properties of the people, and the internal order, improvement, and prosperity of the State.[7]

TABLE 1: California Research Laws

Law	Citation
Cancer Clinical Trial Law	Senate Bill No. 37 (2001)[11]
Controlled Substance Research	Health & Safety §11210-11213
Experimental Drugs	Health & Safety §111515-11545, 111595
HIV or AIDS Research	Health & Safety §121075-121125
Labeling of Investigational Drugs	Bus. & Prof. §4070-4078
Marijuana Research	Health & Safety §11478-11481
Prisoners as Research Subjects	Penal §3501-3509.5
Protection of Human Subjects in Medical Experimentation Act	Health & Safety §24170-24179.5
Stem Cell Research	Health & Safety §125118-125119.5

Activist California Fills Federal Void

California has broadly exercised its right to legislate in those areas not preempted by federal law (see Table 1). One example of a California law that complements federal regulations is the California Protection of Human Subjects in Medical Experimentation Act. The Research Subjects' Bill of Rights is codified at §24171 of this act, and is also referred to as the "experimental subject's bill of rights." There are 10 elements to the California Research Subjects' Bill of Rights, including the subject's right to:

(a) Be informed of the nature and purpose of the experiment.

(b) Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

(c) Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.

(d) Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

(e) Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.

(f) Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

(g) Be given an opportunity to ask any questions concerning the experiment or the procedures involved.

(h) Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

(i) Be given a copy of the signed and dated written consent form as provided for by Section 24173 or 24178 [of the Act].

(j) Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

A copy of the California Research Subjects' Bill of Rights must be provided to the subject in a language in which the subject is fluent "prior to consenting to participate in any medical experiment [containing the 10 elements above] and the copy is signed and dated by the subject [or the subject's legally authorized representative (LAR)]."[8]

In addition to that bill of rights, the California research subject (or LAR) must be informed "both verbally and within the written consent form" of the following: if the research involves a placebo; risks and discomforts; benefits; alternative procedures; expected recovery time; opportunity to ask questions; right to withdraw; name, institutional affiliation, and address of the principal investigator; name of the sponsor or funding source; impartial third party to address complaints; and any material financial stake or interest of the investigator or institution.[9]

The California Protection of Human Subjects in Medical Experimentation Act carries financial and criminal penalties when medical research is conducted without consent or without communicating known risks and hazards. Negligent failure to obtain informed consent is subject to a monetary fine between $500 and $10,000.[10]

Willful failure to obtain informed consent is subject to a fine between $1,000 and $25,000, and if the subject is exposed to a known substantial risk of serious injury, the maximum fine increases to $50,000, in addition to possible imprisonment for up to a year.[10]

If a representative or employee of a sponsor knows of a risk or hazard and willfully withholds information of the risk or hazard from the researcher, and thereby exposes a subject to substantial risk of serious injury, this individual is subject to a possible monetary fine of $50,000 or imprisonment of up to a year.[10]

Beyond California

Research in the United States is governed by a vertical hierarchy of laws, with federal statutes at the top and federal regulations immediately below, followed by noncompeting state laws. Horizontally, the 50 states and the territories of the United States have non-overlapping laws that govern research within their borders. This patchwork results in a fragmented web of regulations and regional differences in the operationalization of a multicenter, multistate clinical trial. California is just one example of a state with a variety of laws that impact the clinical research professional.

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10. California Health & Safety Code § 24176.
11. Codified at §1370.6 of the Health & Safety Code; §10145.4 of the Insurance Code; and §§14087.11, 14132.98 and 14132.99 of the Welfare & Institutions Code.

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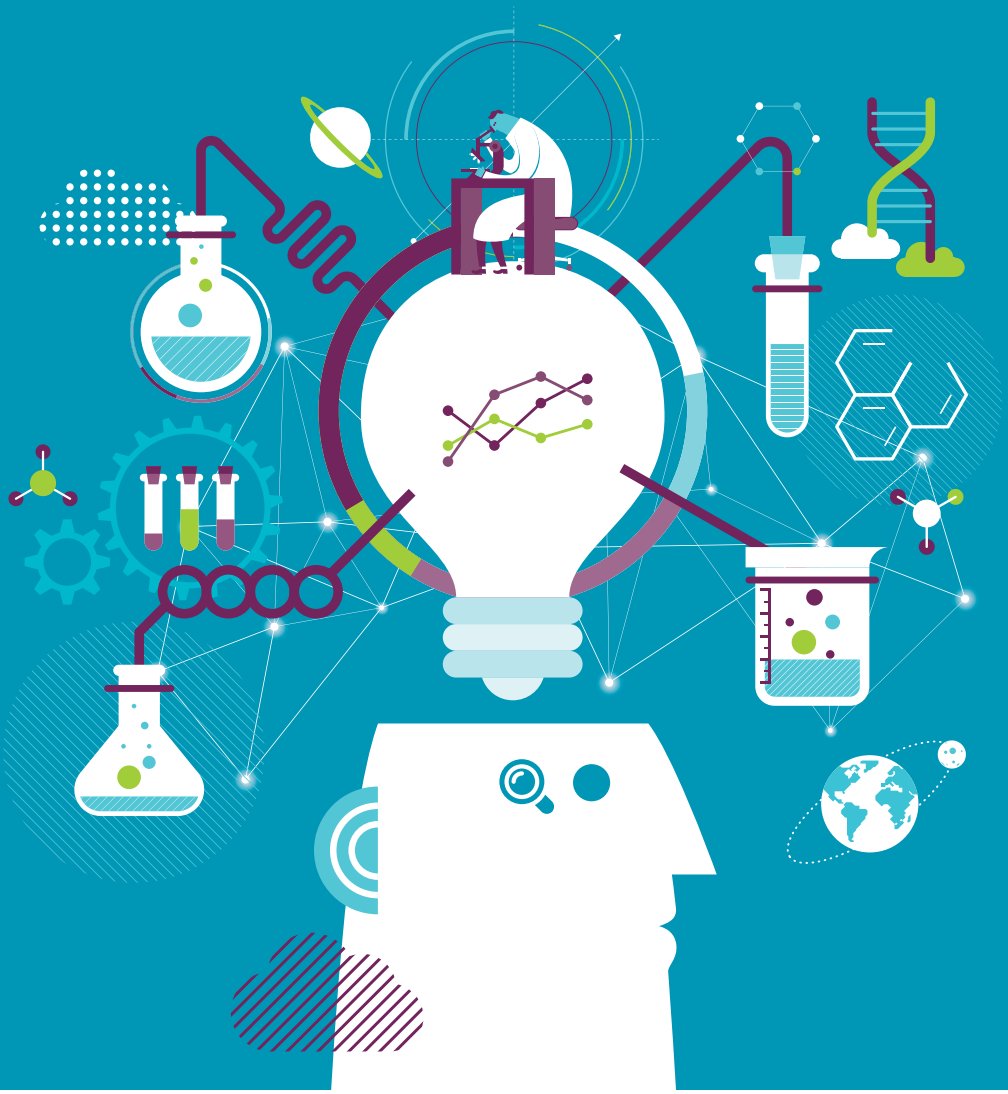
Making Room for **Research *in* the Box**



"Research outside the box" is all about doing something different. It implies improving our processes by changing how we think and how we view the same problem.

Often, innovation happens fastest when people from outside a given industry are able to bring the common, well-accepted viewpoints of their industry to an industry where those viewpoints are foreign. All too often, what is obvious common sense to one industry is unheard of in another.

So what is "the box"? I'm going to define "the box" as healthcare, and I want research inside the box. That box is normal medical practice, and I want research conducted in every medical practice everywhere.

On the Outside Looking In

Throughout most of the world, research is a separate endeavor from normal medical practice. If research activities exist at all, they are typically performed by a separate department and are viewed as a sidelight, hobby, or even a stepchild. Further, the vast majority of all medical practice has no associated research activity whatsoever; that includes large group practices, multispecialty practices, hospitals, and other healthcare facilities.

So let's place ourselves in another industry. Imagine that we are beta testing software in the information technology (IT) industry; we have to be able to continue to research our software, to get smarter, and to determine where the major bugs are in our software long before we launch our software. In essence, we have to determine what the side effect profile is of our software running in different operating system environments.

Given this challenge, we create a very low barrier to entry for beta testers. We have to make it very attractive for beta testers to want to use our software and to get engaged in our work. They get the cutting edge of our technology, but they have to report back on how it performs. Perhaps we even receive automatic reports of performance metrics.

What is commonplace in the software industry is somewhat foreign in the research industry; we make it very difficult for anyone to get involved in research. It's not merely the case that the person has to be demonstrably competent at a variety of complex skills before we even let them engage in studies, but we put up numerous unnecessary barriers to involvement in research and find all sorts of ways to waste the time and effort of our investigative teams.

Also, we make it very difficult for anyone to stay involved in research. We create so many hurdles that even intelligent, successful researchers throw in the towel and opt to simply become a medical clinician. As a result, research is conducted at very few facilities, with only a tiny fraction of patients ever becoming involved. This is why it takes a decade for the research to be conducted—a time frame that would be absolutely inconceivable in the IT sector. Unfortunately, that's what we too often settle for when it comes to medical research.

Getting Up to Speed

Certainly medical research is different from researching software. I get that. Certainly, we have reasons for moving more slowly; for one, there's more at stake. However, there's no reason whatsoever that it should take a decade or more to bring most of our effective new products to market.

I think we can all agree that if research was embedded in every medical practice everywhere, the speed of medical research would accelerate to something we don't even dream of today.

So what is "research inside the box"? It is research that is embedded in medical practice itself. It is a philosophy that research is as critical a component of medical practice as medical care.

We are not operating in the Middle Ages; medical innovation cannot happen without research. Without it, we would still be using the antiquated treatments we used 20, 30, even 50 years ago. For any of us with more than 10 years of practice under our belts, it's easy to think back and recall how we practiced such a short while ago. It's easy to recognize the innovations that have happened in such a short period of time and how they have altered our practice behavior for the better.

Still, research is agonizingly slow, partly because only a mere fraction of physicians participate, and an even smaller percentage of those stick with it. Most patients have no idea how this process occurs, and most patients are never offered research opportunities despite being qualified.

We know that research is the only way innovation can flourish, and we should be 100% certain that we must get smarter, so that 10 years from now, we can be treating patients better. We also know that 96% of patients who participate in research enjoy the process, and would agree to participate again. Then why wouldn't we integrate research into literally every medical practice, every medical specialty, and every hospital in the world?

Calling All Champions

I realize it's like swimming upstream. Everyone's too busy. Everyone's too stressed. Everyone's too heavily regulated already. Most practices and large healthcare facilities view adding research as a burden—or as a sideline activity that is "nice to have," but unnecessary.

Therefore, adding research requires a champion. It requires somebody willing to fight this fight, and the fight isn't easy. It requires somebody willing to advocate it every day for as long as it takes. That's a tall order, but the benefits could be massive.

So what is "research inside the box"? It is research embedded in the medical practice itself.

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Jamie Meseke, MSM, CCRA

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Mary Anne Kennedy, CCRC,
on managing career turns, the value of certification, and how to improve subject safety

Q: How did you first become interested in clinical research, and can you describe the career path you've followed?

A: I became interested in research when I tried to manufacture soap in science class. I wanted to know the "what," "how," and "why." After college, I started a job as a non-critical editor for a bibliographic database service. I reviewed peer-reviewed journals covering preclinical and experimental research, methods, and instrumentation in disciplines like botany, microbiology, and pharmacology. The job piqued my curiosity about research in general.

Later, I went to work in the pharmacy at a level 1 trauma center affiliated with a university medical college in Florida. I got to know some of the monitors who came in to reconcile study medications; they told me how rewarding the field of clinical research was to them, and I was intrigued.

When the hospital opened a clinical research unit, I moved into a new position as a coordinator/regulatory specialist. There were many exciting research studies going on, and I felt like I had found my place.

Q: Your career has taken a few turns. Can you tell us a bit more about where you started, and the different types of roles you've held?

A: At first, I was doing coordinator tasks, but I became interested in regulatory duties and eventually I served as a communications liaison between sponsors, principal investigators (PIs), and our institutional review board. I also maintained regulatory binders and assisted with site visits.

Later, after moving to Wisconsin, I took a position with a clinical research group specializing in asthma, allergies, and pulmonary diseases. I aided in subject recruitment and helped maintain a database of potential subjects. I also assisted with site feasibility questionnaires, visits, and training new coordinators about regulatory requirements. I had the opportunity to work with doctoral fellows, and it was satisfying to see some of them become PIs in their own right.

I currently work for the Office of Clinical Trials at the University of Wisconsin. Our office provides regulatory services for investigators in various disciplines who are leading industry-sponsored trials, federal grants, investigator-initiated studies, or foundation-sponsored trials.

In all of my experiences, I am still asking "what," "how," and "why."

Q: When did you first get involved with ACRP? What type of benefits have you reaped from being a member?

A: A monitor mentioned ACRP to me early on, and suggested that I look into taking some of the courses. I heeded her advice and attended an onsite "Fundamentals of Clinical Research" course in Alexandria, Va. The course provided me with a great introduction to clinical research and added to my core knowledge. I went back to my job feeling empowered by what I had learned.

I felt lucky when I joined the asthma and allergy clinical research group, as its leadership valued education for the staff. That team encouraged me to take the Certified Clinical Research Coordinator (CCRC®) exam and to maintain my certification. My certification demonstrates to PIs, monitors, and sponsors that I take my role as a clinical research professional very seriously, and that I will try to the best of my ability to maintain the safety and rights of study subjects.

My certification is a formal recognition that my skills and knowledge base are current. By maintaining my certification, I am continuing to learn and hone my skills. I believe that it is reassuring for PIs and sponsors to know that the people they have entrusted to perform their research have the commitment and training to do so in a professional and ethical way.

Q: Since you have been in the industry for a while, you have no doubt seen many changes. What are the most significant changes you have seen?

A: I think the public's perception of clinical research has changed over the years. More people seem to view clinical research in a positive light, and many of them have participated in a clinical trial. I think the recent news stories on Ebola and the therapies that are being developed have enabled more people to understand the need for and benefits of clinical research.

I also think research subjects are more informed, which is a good thing. They are more engaged. They ask the "what," "how," and "why" questions.

Q: What advice do you have to share with other clinical research professionals, in terms of professional development and advancement?

A: I would encourage clinical research professionals to stay current in their field and stay passionate about what they are doing. Learn as much as possible from each job. Those people who go above and beyond are always remembered. High-quality work gets noticed.

Of course, don't be afraid to network. Chat with monitors, other study coordinators, and medical professionals, as they can be a source of friendships and mentors.

Q: As you think about the future generation of clinical research professionals, what "lessons learned" would you like to share?

A: First, I would encourage any future clinical research professional to keep learning and understand why you are working in the field.

Second, do not lose sight of why you entered this field—be open to the new things around you. The job can get difficult, but know what you are doing is important.

Third, do not forget to laugh and be joyful. There may be a lot of people counting on you and your deadlines may be approaching, but take time to share a laugh. Everyone appreciates a kind word or smile.

I believe that it is reassuring for PIs and sponsors to know that the people they have entrusted to perform their research have the commitment and training to do so in a professional and ethical way.

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Margo Michaels, MPH

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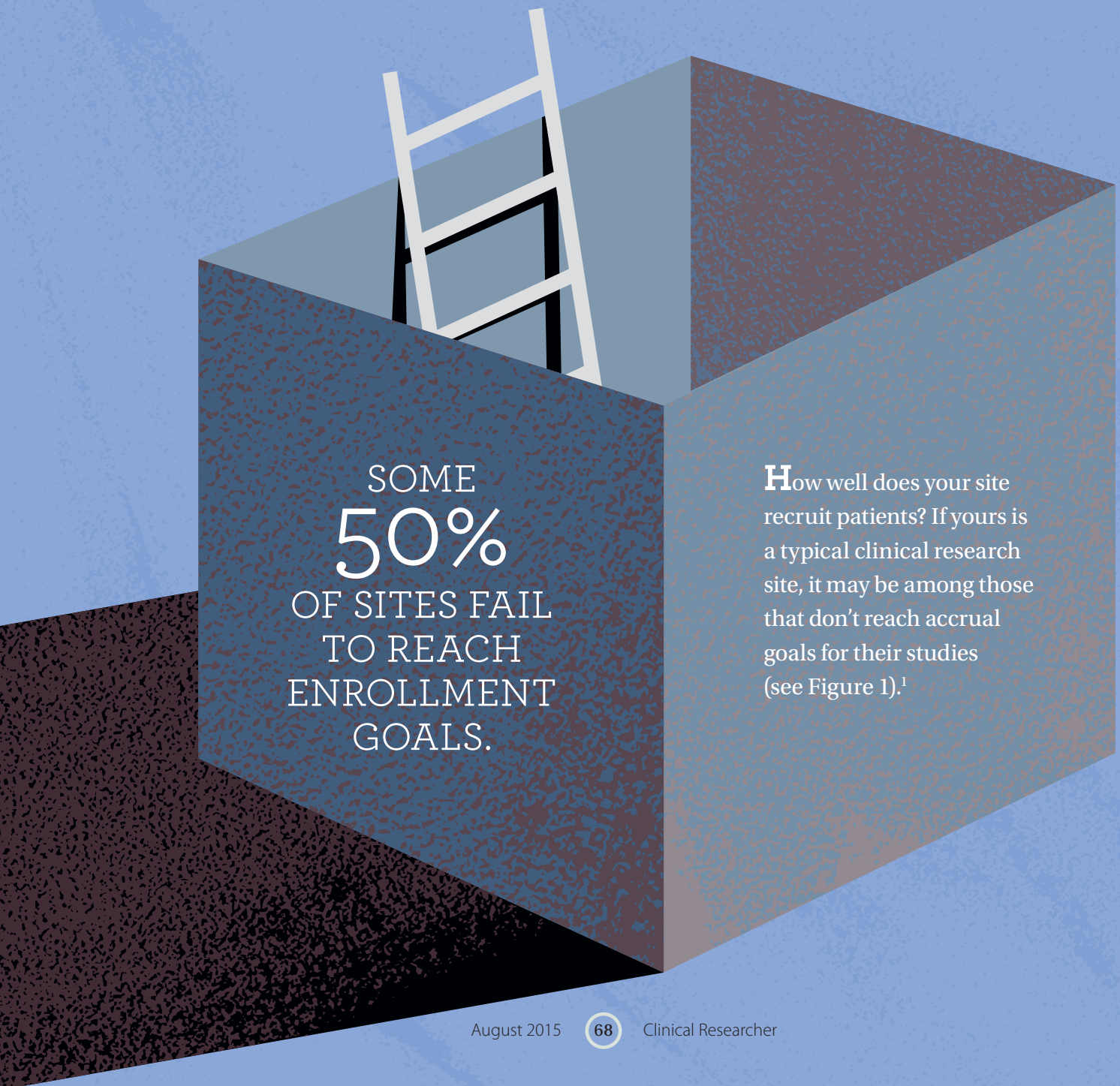
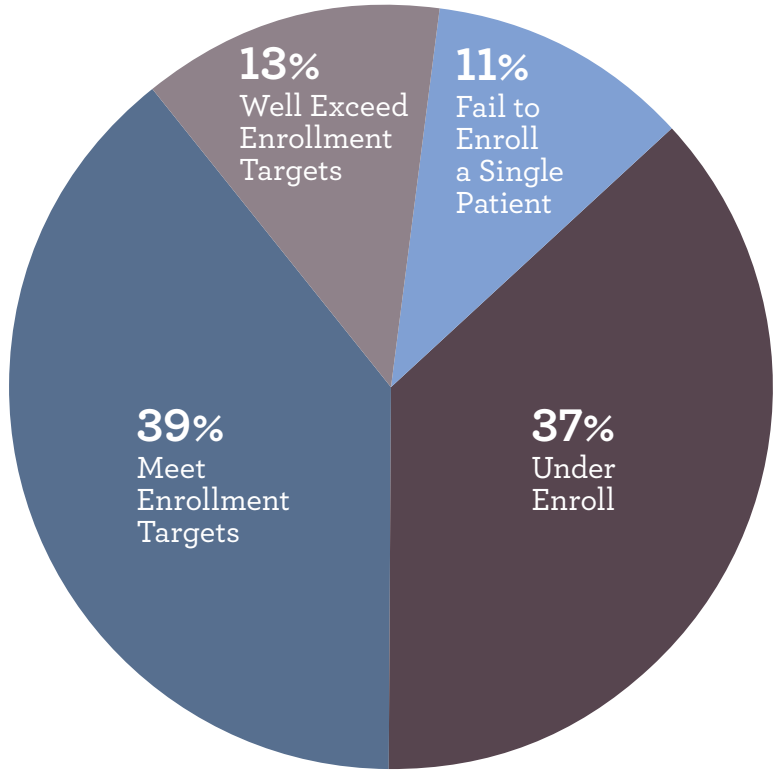
RECRUITMENT Outside the Box



How well does your site recruit patients? If yours is a typical clinical research site, it may be among those that don't reach accrual goals for their studies (see Figure 1).[1]

FIGURE 1: Investigative Site Enrollment Performance



(N=15,965 sites participating in 153 global Phase II and III clinical trials) *Source: Tufts CSDD, 2011*

Share the questions found in Figure 2 about the effort that goes into subject recruitment with your colleagues to see what other members of your research team think about these issues.

If you answered "OK" or "Not Very" to more than three of these questions, your site may need to start thinking "out of the box." Figures 3 and 4 provide some community and physician education tips to get you thinking about changes you can make. (Next issue, we will revisit this question to talk about road-tested policies and procedures.)

FIGURE 2: Recruitment-Related Questions for Sites to Consider

Question	Very	OK	Not Very
1. How consistent are our referrals from outside providers?	☐	☐	☐
2. How well do we communicate with outside providers about the clinical trials we offer? *(Important point: A "Dear Colleague" letter/list of trials does not count as quality communication!)*	☐	☐	☐
3. How well do we communicate with our referring providers about clinical trials as a quality treatment option?	☐	☐	☐
4. How well do we communicate with our community about clinical trials as a quality treatment option? *(Important point: Attending health fairs does not count as quality communication!)*	☐	☐	☐
5. How well are clinical trials integrated into the outreach and community relations efforts at our site?	☐	☐	☐
6. How well can other medical, clinical, or administrative staff at our site provide appropriate information and encouragement about clinical trials?	☐	☐	☐

For more information on topics related to this column, please visit the ACRP Clinical Trials Recruitment Interest Group online at acrpnet.org/IG-recruitment

FIGURE 3: Community Education Tips

Principle	Apply it by…
Don't promote particular trials in outreach or education programs	☐ Emphasizing the fact that your institution provides quality options for care, including clinical trials *In general, it is not a good idea to undertake community-based recruitment efforts for any trial, especially in a treatment setting.*
Recognize that the educational needs of the general public differ from those of an individual facing a treatment decision	☐ Developing collaborative relationships with community groups and their leadership around educational programming and community outreach, focusing on the quality care you provide through clinical trials ☐ Offering interactive learning opportunities with local community groups (e.g., civic clubs, churches, and disease/condition support groups)[2] ☐ Supporting efforts to educate community about benefits of clinical trial participation as an option for care ☐ Using social marketing techniques emphasizing quality care at the site and quality care through clinical trials ☐ Providing appropriate and current information regarding open disease/condition clinical trials for the public in a visible, easy-to-use, web-based format ☐ Hosting an "Aware for All"–type event (see https://www.ciscrp.org)
Create actionable messages and related products for public (non-patients)	☐ "When someone you love is told they have (insert disease/condition), we need to make sure they understand all their options for treatment." ☐ Use easy-to-understand flyers or brochures with phone numbers that are evergreen ☐ Consider bringing "trinkets" as a way to promote your practice and clinical trials
Don't make assumptions about community attitudes toward clinical research	☐ Finding ways to present clinical trial information that complement the values people in the community hold. These may include access to care, social justice, importance of contributing to research, etc. *For minority communities in particular, the legacy of abuses in research should not be overlooked, but check your assumptions about mistrust about or lack of interest in research before beginning an educational program. Attitudes vary widely.*
Use peer-to-peer education approaches	☐ Training community leaders and/or past trial participants to become "Clinical Trial Ambassadors" *Using peer education (e.g., training community leaders to become community educators about clinical research) may be more successful than solely using research staff as educators.*
Use education as part of a long-term institutional effort to generate trust and quality care	☐ Demonstrating that your site is "in for the long haul," and is not just interested in recruiting patients for a particular clinical trial; think about other services your practice can provide ☐ Being open to learning about community needs to enhance access to care; for example, it may be helpful to incorporate evening and weekend hours into required trial visits ☐ Visibly supporting efforts of community partners to promote disease/condition screening ☐ Promoting ready access to disease/condition screening to help reduce health disparities and as a way to promote quality disease/condition care ☐ Developing systems that build trust and enhance communication at the community level ☐ Developing a Community Engagement Program in clinical research/quality care for all; for example, create a community advisory board to enhance local community support for research, and to help you create more accruable trial menus
Don't base "success" of educational programs on accrual alone	☐ Measuring increases in inquiry or changes in knowledge, attitudes, or behavioral intent
Use appropriate promotional language about research	☐ Emphasizing importance and availability of quality care and treatment options offered through clinical trials Message: Quality of Care *Example: "Therapies offered through cancer clinical trials should be considered the preferred treatment choice for physicians and patients, if they are available." (National Comprehensive Cancer Network, 2008)* Message: Access, social justice, generalizability *Example: Physicians should "strive to make participation in clinical trials a key component of clinical practice and to achieve. . .high accrual rates of 10% or more." (Institute of Medicine, 2010)*

FIGURE 4: Referring Provider Education Tips

Principle	Apply it by
Don't promote particular trials	☐ Emphasize the fact that your institution provides high-quality options for care for patients, including clinical trials (in these areas)… *In general, it is not a good idea to undertake any "Dear Colleague"–like efforts on any specific trials.*
Build collaborative relationships	☐ Reaching out to referring physicians where relationships are already established ☐ Providing educational opportunities to inform providers about the importance and availability of quality care and options offered through clinical trials ☐ Offering detailing/"lunch and learns"/grand rounds for referring physicians • Keep presentations brief • Address whole staff, not just physicians ☐ Developing reliable referral systems for clinicians who diagnose (the conditions you are studying) to expedite site access for patients ☐ Developing business agreements with local practices to allow researchers to pre-screen patients ☐ Publishing reports, a newsletter, or letters outlining research activities and periodically disseminate them to local providers ☐ Hiring navigators or translators as a part of clinical and research teams ☐ Developing a clear policy to maintain communication with the referring providers to keep them informed about their patients

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1. Tufts Center for the Study of Drug Development. 2011.
2. McKinney MM, Weiner BJ, Carpenter WR. Building community capacity to participate in cancer prevention research. *Cancer Control.* 2006;13(4):295-302

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If accepted for publication, articles are published in the next available issue, although some submissions may be held for use in an issue that presents many articles on the same theme. Note, however, that the EAB will review **any** article on **any** clinical research topic **any** time it is submitted.

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