CenterWatch Weekly

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Factors to Consider in PI Compensation and Consequences of Getting It Wrong

By Leslie Ramsey

When it comes to deciding how to compensate principal investigators (PIs), sites have three factors to consider and getting them wrong carries a high cost, says one expert.

The first challenge is determining the fair market value of the work performed, says David Russell, director of site strategy at WCG PFS Clinical. "There's not an answer that you could just go to and say 'what is a fair market value for a particular specialty,'" Russell says.

The days of offering enrollment incentives to PIs are in the past, Russell says. "There shouldn't be anything that would be viewed as an incentive to enroll more patients than what would normally qualify." If a PI is paid above fair market value, the institution providing the payment runs the risk of federal scrutiny for possible violation of the Stark Law.

The Stark Law prohibits physicians from making referrals for Medicare-payable services if the physician or an immediate family member stands to gain financially. And it prohibits the organization employing the physician from billing Medicare or other payer for those services.

To protect itself from Stark Law violation, Russell says an institution must set up a personal service arrangement — a PI payment agreement — with a PI that specifies the services covered by the compensation and sets the level of compensation in advance. The key to this Stark Law exception is avoiding basing compensation on the volume or value of

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Focus on Skills Rather than Roles or Systems in Training Trial Pros, Experts Say

By Brandon May

Clinical trial managers need to focus training on skills, not systems or roles, to bring much-needed improvement to clinical trial performance.

"I love the idea of being able to train people, and I think the direction of that training is moving from being system- and role-based to being skill-based," said David Burrow, director of the office of scientific investigations and office of compliance at the FDA's Center for Drug Evaluation and Research.

"If you teach people the skills they need to be able to effectively navigate the tools and technologies and processes," he said, "those skills will be critical as those tools and technologies and processes begin to change over time." Burrow spoke last week at the SCOPE summit in Orlando, Fla.

Teaching someone just one tool, technology, or process without the associated skills that help that person navigate these items, he added, is training that is not extensive or scalable for the longer term.

Jim Kremidas, executive director of the Association of Clinical Research Professionals (ACRP), said there are three key elements that play a role in improving site performance: technology, processes and training. Training, he says, may be the most important element in terms of predicting and improving site performance. "People don't typically go to college and dream about entering this industry and becoming

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Industry Briefs

Trials Not Operating at Best Practice Levels, Survey Says

Sixty-five percent of clinical operations teams responsible for managing and overseeing trials don't see themselves operating at best practice levels when it comes to identifying issues quickly, according to a new survey about trial oversight.

A new survey conducted by Medidata and Informa Pharma Intelligence cites trial complexity, increasing workloads with fewer resources, growing amount of data needing to be captured and evaluated, and rising difficulties in patient recruitment as reasons why they're struggling to prioritize their responsibilities.

Another key drag on the ability to successfully run trials, respondents complained, is that they're mired in tasks that don't advance the goals of the trial. When asked where they focus their time, almost half of respondents stated that at least 25 percent of their time was spent on tasks and issues with minimal impact on outcomes.

Only 2 percent of respondents claimed to have completed all their tasks on time; 25 percent of respondents completed 75 percent to 99 percent of tasks on time; and another 48 percent only completed 50 percent to 74 percent of their tasks on time.

To read the survey, click here: https://bit.ly/38RFAlc.

NLM Seeks Input on Improving ClinicalTrials.gov

ClinicalTrials.gov users will have a chance to weigh in on strategies for improving the database at a public meeting scheduled for April 30.

The National Library of Medicine (NLM), which administers ClinicalTrials.gov, is looking for examples of new uses of the ClinicalTrials.gov website, resources for linking from ClinicalTrials.gov and specific examples of how the website is currently used.

NLM seeks input on initiatives, systems or tools for improving the submission process for ClinicalTrials.gov and ways to enhance information quality and content. In addition to participating in the meeting, stakeholders can provide written feedback by March 14.

Read the NLM's notice here: https://bit.ly/2PfdWXz.

Addendum to ICH Trial Guidelines Offers Recommendations for Statistical Analysis

Effective July 30, an addendum to the International Council for Harmonisation's (ICH) trial guidelines will provide phase 3 trials in the EU with new recommendations for statistical analysis.

The addendum defines the appropriate use of estimands and sensitivity analyses in clinical trials. An estimand is the treatment effect of interest in a clinical trial. The guideline also discusses the impact of estimands on clinical trial design and conduct.

To read more about the guidance, click here: https://bit.ly/2T62PB3.

FDA Compiles Drug Approval Data into Searchable Format

The FDA has launched a compilation of drug approval information in a searchable data file for public use, the agency announced last week.

The dataset on new molecular entities and biologic approvals draws from the FDA's internal databases and document records, presenting data in a downloadable data file.

The first edition of the compiled data includes drugs approved between Jan. 1, 1985, and Dec. 31, 2019. It will be updated periodically to include the latest drug approval data.

Access the compilation here: https://bit.ly/39M0imu.

Health Canada Announces It Will Accept Submissions in eCTD Format

Health Canada has announced that it will accept clinical trial submissions in an electronic Common Technical Document (eCTD) format, an announcement that comes following the completion of a successful pilot of the eCTD in August.

Based on this pilot, Health Canada says that the implementation of clinical trial regulatory activities in the eCTD format will now immediately begin for preclinical trial application consultation meetings, clinical trial applications (CTAs) with a seven-day administrative or a 30-day default performance standard, CTA amendments with a seven-day administrative or a 30-day default performance standard and CTA notifications.

The Canadian public health organization says that use of the eCTD format is optional for clinical trial regulatory activities. If the eCTD format is used, sponsors must submit all regulatory transactions using the Common Electronic Submissions Gateway.

Related instructions and guidance documents on using the eCTD format can be found here: https://bit.ly/2Vb08AV.

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Up and Coming

This feature highlights changes in clinical trial organizations' personnel.

Anika Therapeutics

Cheryl Blanchard, a member of Anika Therapeutics' board of directors, has assumed the role of the interim CEO following the death of the company's CEO Joseph Darling. Anika is currently in the process of looking for a new CEO.

Aprea Therapeutics

Aprea Therapeutics has appointed **Gregory Wessels** to a newly created position of vice president of commercial. Prior, Wessels served as executive director of U.S. marketing for lymphoma and acute myeloid leukemia at Bristol-Myers Squibb.

AskBio

AskBio has appointed **Anna Tretiakova** as the firm's new senior vice president of product development. Tretiakova's most recent focus was in gene therapy at Swan Therapeutics.

Endo International

Blaise Coleman will succeed Paul Campanelli as president and CEO at Endo International. Coleman has served as Endo's executive vice president and chief financial officer since 2016.

Enterprise Therapeutics

Enterprise Therapeutics has named **David Morris** as the company's new chief medical officer. Morris was most recently managing director at the Novartis Venture Fund, where he will remain as an operating partner.

Everest Medicines

Everest Medicines has found its new CEO in Eli Lilly veteran **Kerry Blanchard**. Prior to this appointment, Blanchard was senior vice president of China drug development at Eli Lilly.

Evolution Health Group

Evolution Health Group has named **Michael Stevinson** executive vice president of the communications firm's blulava division. Most recently, Stevinson was executive principal and managing director at ICON.

George Clinical

Australia-based George Clinical named **James Cheong** as its new CEO. Cheong was most recently head of clinical operations of the Chinese market for Boehringer Ingelheim.

Gilead Sciences

Michael Quigley is now senior vice president of research biology at Gilead Sciences. Prior to joining Gilead, Quigley served as Bristol-Myers Squibb's vice president and head of the tumor microenvironment modulation thematic research center and site head of the Redwood City, Calif., location.

Hua Medicine

Fuxing Tang has been appointed to the role of chief technology officer and vice president of formulation R&D and product development at Hua Medicine, joining the company after most recently serving as director of pharmaceutical sciences at Teva Pharmaceuticals.

Immunomedics

Loretta Itri has joined Immunomedics as its new chief medical officer. Previously, Itri oversaw global health sciences and medical affairs at The Medicines Company.

Kura Oncology

Antonio Gualberto, founder and chief medical officer of early-stage biotech Kura Oncology, has been tapped as Eisai's H3 Biomedicine's chief medical officer.

Lyndra Therapeutics

Lyndra Therapeutics has named **Richard Scanton** the company's new chief medical officer. Prior to this appointment, Scranton was chief medical officer at Pacira Pharmaceuticals.

Rentschler Biopharma

Rentschler Biopharma has tapped **Grace Kim** as the company's vice president of business development - North America and APAC, a newly created position within the organization. Recently, Kim was vice president at Northway Biotechpharma.

Sofinnova Partners

Robert Carroll has been appointed to the roles of partner and head of investor relations at Sofinnova Partners. Prior to this appointment, Carroll co-led PwC's global fundraising advisory platform.

Sophia Genetics

Philippe Menu has been named chief medical officer of Sophia Genetics, joining the company after most recently serving as a leader in the McKinsey Cancer Center.

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Factors to Consider

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referrals or other business generated between the parties, he says.

"I can't stress enough how much to really go over the amounts with the physician, discuss with the physician why you're paying them this amount of money," Russell says. "Get their buy-in."

The third consideration in determining PI compensation is the federal Anti-Kickback Statute (AKS). "This is really where I think your principal investigator is going to be the most interested because this is a criminal statute that is on the books."

The statute is similar to the Stark Law, Russell says, in that it prohibits "knowing and willful" solicitation, receipt or offer of remuneration for referring, recommending, leasing or ordering of items or services to Medicare or Medicaid beneficiaries. As with the Stark Law, there is a "safe harbor" institutions can use to avoid criminal charges. If the activity is within the parameters of a written and signed personal service agreement and holds to fair market value, it is allowed, he says.

The provision in the anti-kickback safe harbor that institutions often miss, according to Russell, is that the agreement has to be for no less than 12 months. Even if a trial will last only six weeks, he says, the agreement still has to be for 12 months and terms can't be changed in that period.

"I can't stress enough how much to really go over the amounts with the physician, discuss with the physician why you're paying them this amount of money. Get their buy-in."

—David Russell, director of site strategy at WCG PFS Clinical

"So in other words, if a physician says, well, I feel like my fair market value is higher, you can't go back and increase the rates," he says. "You can't go back and lower either."

The penalties for violating either the Stark Law or the anti-kickback statute are steep, Russell warns. Stark Law penalties can range from simply being denied payment for the designated health service to complete exclusion from the Medicare or Medicaid program and/or state healthcare programs. Monetary penalties can be high enough to break an institution. They start at a fine of up to $15,000 for each service that an institution "knows or should know" was provided in violation of the law. Other fine amounts could be three times the total amount of the improper payment received from Medicare or up to $100,000 for each effort to circumvent the law.

Penalties for anti-kickback violations could include fines, jail terms or exclusion from participation in federal healthcare programs. PIs who accept kickbacks could be fined up to $50,000 per kickback plus three times the total amount of the money received.

Russell recommends explaining the consequences of crossing these lines to PIs who push for increased compensation. "When you feel as an institution that would put you outside the parameters of your fair market value, you probably need to go over the anti-kickback statute and the Stark Law with the physician just to tell him what those ramifications are because it affects him or her specifically."

Features

Focus on Skills

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a clinical researcher," he said. "Rather, people are trained into the roles they play, but there is no consistency in processes, especially at the site level."

Variance within the industry, particularly in regard to training and how investigators create and conduct protocols, can create challenges in site performance. Kremidas said that there is a need to define the competencies required of study coordinators, for principal investigators (PIs) to efficiently conduct protocols. "If we define those competencies, get industry alignment around those competencies and ultimately validate the people doing the research who have those competencies," he said, "that would be a quantum leap in our ability to deliver good-quality research to the world."

Kremidas noted that approximately 17 percent of study coordinators in the ACRP database don't have a four-year college degree, whereas 10 percent of coordinators have PhDs. "That's not to say one is better than another," he said, "but it does suggest that there's currently a great deal of variance in terms of the qualifications of most study coordinators." Kremidas added, "When we start talking about how to predict site study performance, we're going to suggest that we need to look at the site staff beyond the PI." The regulatory definitions for training currently remain arbitrary, and the qualifications necessary for study coordinators are virtually nonexistent.

"I love the idea of being able to train people, and I think the direction of that training is moving from being system- and role-based to being skill-based."

—David Burrow, director of the office of scientific investigations and office of compliance at the FDA's Center for Drug Evaluation and Research

Sites should be more diligent about checking to see if coordinators are certified by either the Society of Clinical Research Associates or ACRP. If sites do that consistently during feasibility assessments, he said, the industry will begin to see more people move toward getting certification. "Plus," added Kremidas, "certification of study coordinators and/or the PIs is typically associated with faster study startup, faster enrollment and fewer protocol deviations."

In terms of site quality assessment, Jonathan Rowe, associate principal at ZS Associates, suggested that staff retention could be an important predictor. He and his colleagues at ZS recently examined over 700 studies to identify characteristics that drive study quality and risks. Study attributes included in the model were study therapeutic area, phase, participant count, protocol deviations and protocol amendments. "When it comes to predicting site quality, one of the things that really stood out to me in this model was staff turnover," said Rowe, "which was not just at the site but was also at the level of the CRO and the sponsor."

According to Rowe, risk management represents an essential component of better-performing sites. "We should be developing risk plans and communicating these plans between sponsors, CROs and sites," he commented. Burrow echoed Rowe's statements, suggesting sites should have systems in place that can detect risks and can correct errors in real time. "I love the idea of making errors more visible at sites," he added, "because that often means they will be quickly addressed."

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status	Sponsor Contact
Atreca	ATRC-101	Select solid tumor cancers	phase 1 first patient dosed	atreca.com
AXIM Biotechnologies	cannabinoid-based chewing gum with dronabinol	chemotherapy-related symptoms	phase 1 completed	AXIMBiotech.com
Applied Genetic Technologies	AGTC-501	X-linked retinitis pigmentosa	phase 1/2 enrollment completed	agtc.com
Molecular Templates	TAK-169	relapsed/refractory multiple myeloma	phase 1 dosing initiated	mtem.com
Cyclo Therapeutics	Trappsol Cyclo	Niemann-Pick disease Type C	phase 1/2 patient enrollment completed	cyclotherapeutics.com
Harbour BioMed	HBM9161	autoimmune diseases	phase 1 completed	harbourbiomed.com
ImmunogenX	Latiglutenase (IMGX003)	celiac disease	phase 2b enrollment started	immunogenx.com
Aravive	AVB-500	platinum-resistant recurrent ovarian cancer	phase 1b enrollment started for higher dosage	aravive.com
BioXcel Therapeutics	BXCL501	agitation in schizophrenia	phase 2 trial initiated	bioxceltherapeutics.com
RIBOMIC	RBM-007	exudative age-related macular degeneration	phase 2 first patient injected	ribomic.com/eng/
DelMar Pharmaceuticals	VAL-083	newly diagnosed, MGMT-unmethylated glioblastoma multiforme	phase 2 final patient enrolled and dosed	delmarpharma.com
Palatin Technologies	topical PL9643	dry eye disease	phase 2 initiated, first patient enrolled	palatin.com
Compugen	COM701, in combination with nivolumab and BMS-986207	advanced solid tumors	phase 1/2 plans for initiation	cgen.com
Dyve Biosciences	DYV-700	acute gout	phase 2 initiated, first patient enrolled	dyvebio.com
VBL Therapeutics	VB-111 in combination with nivolumab	metastatic colorectal cancer	phase 2 initiated	vblrx.com
SCYNEXIS	ibrexafungerp	vulvovaginal candidiasis	phase 3 enrollment completed	scynexis.com
Isofol Medical	arfolitixorin	metastatic colorectal cancer	phase 3 first patient in Japan dosed	isofolmedical.com
Alnylam Pharmaceuticals	vutrisiran	ATTR amyloidosis	phase 3 enrollment completed	alnylam.com
Axsome Therapeutics	AXS-007	migraines	phase 3 enrollment completed	axsome.com
Epizyme	TAZVERIK (tazemetostat)	follicular lymphoma	priority review granted by the FDA	epizyme.com
Seattle Genetics Astellas Pharma	PADCEV (enfortumab vedotin-ejfv)	advanced bladder cancer	Breakthrough Therapy designation awarded by the FDA	seattlegenetics.com astellas.com/en
Cardiovalve	Transcatheter Tricuspid Valve Replacement System	tricuspid regurgitation	Breakthrough Therapy designation awarded by the FDA	cardiovalve.com
Horizon Therapeutics	PROCYSBI (cysteamine bitartrate)	nephropathic cystinosis	new dosage form approved by the FDA	horizontherapeutics.com
Agile Therapeutics	Twirla (levonorgestrel and ethinyl estradiol) transdermal system	female hormone deficiency	approved by the FDA	agiletherapeutics.com
Baudax Bio	ANJESO (meloxicam injection)	management of moderate to severe pain	approved by the FDA	baudaxbio.com
Bristol-Myers Squibb	Opdivo (nivolumab)	unresectable advanced or recurrent esophageal cancer that has progressed following chemotherapy	approved by the Japan Ministry of Health, Labor and Welfare	bms.com

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