Regulators, Industry Still Have Not Reached Consensus on Risk-Based Monitoring

By Elizabeth Hinkle

Despite more than six years of regulators’ encouragement to adopt risk-based monitoring (RBM) of trials, the industry still has concerns about compliance.

Attendees at a recent FDA workshop question whether RBM is appropriate for small and complex studies, the appropriateness of sampling techniques for source data review (SDR) and source data verification (SDV) and how data privacy regulations might impact transmission and review of trial subject data.

But RBM has been shown to improve data quality, David Burrow, director of CDER’s Office of Scientific Investigations, told attendees at the workshop, also sponsored by Duke University. With companies that have implemented true RBM programs, Burrow said, the FDA has seen a great correlation between issues caught by those plans and problems often flagged in new drug applications.

But challenges — such as customization of RBM to individual trials and regulatory consistency — remain, leaving the industry lukewarm, industry speakers and workshop attendees agreed.

One problem that comes up frequently is a lack of understanding of what RBM means from the FDA’s perspective. RBM is part of an overall quality management plan, not just a component of study monitoring, Burrow said. Companies need to look at

see Risk-Based Monitoring on page 4 »

Sites: Make Financial Audits Work for You

Are you like too many other clinical trial sites? Not getting paid what you think you’re owed, getting checks that you can’t tie to a study or spending too much time resubmitting invoices?

Then you should think about conducting regular financial audits, says David Russell, director of site strategy at PFS Clinical. “Sponsors and CROs are typically not going to remind you to send them invoices or to request the funds that you’ve already agreed to.”

And while it may seem like a lot of work, conducting financial audits can “reap very large rewards in making sure that everything is collected,” Russell told a CenterWatch webinar.

In his experience, payments are made on time and in accordance with the CTA only about 72 percent of the time. And even when they’re paid on time, they often aren’t accurate. “Only about 70 percent of payments are actually paid correctly. That’s a high number, but that means three out of every 10 invoices that you send in, or visit checks that you’re seeing, are inaccurate.”

“This is not saying that sponsors or CROs intentionally are paying inaccurately. Oftentimes I think they’re doing the best that they can. All I can say is, look at it from their perspective. As a sponsor, as a CRO, if there’s a study that’s going on, and we’ll just generalize and say it’s at 40 sites, what that typically means is that there’s 40 different

see Financial Audits on page 5 »
Up and Coming

This feature highlights changes in clinical research organizations’ personnel.

Gilead
Executive shakeup continues at Gilead, where chief scientific officer and R&D head John McHutchison will leave the company next month. Hutchison, a nine-year veteran of the company, stepped into his current position a little more than a year ago. Gilead did not specify a reason for his departure and has not named a successor. Also leaving next month is chief patient officer Gregg Alton, who will serve in an advisory capacity until the end of the year.

MODAG
MODAG has announced the appointment of Torsten Matthias as chief executive officer and Armin Giese as chief scientific officer. Matthias is the owner, CEO and CSO of worldwide operating group Aesku.Group. Giese was formerly the acting head of department at the Center for Neuropathology and Prion Research at Ludwig Maximilian University of Munich.

ObsEva
Elizabeth Garner has been named chief medical officer at Switzerland-based ObsEva SA. Garner most recently served as CMO and head of clinical development at Agile Therapeutics.

RAPT Therapeutics
Dirk Brockstedt has been promoted to chief scientific officer and David Wustrow to senior vice president for drug discovery and preclinical development at RAPT Therapeutics. Brockstedt was previously the senior vice president of biology at RAPT. Wustrow was most recently vice president of discovery at FLX Bio.

CTD
CTD Holdings has named Michael Lisjak as global head of regulatory affairs and senior vice president for business development.

Lisjak most recently served as head of global regulatory affairs for established products and global health at Sanofi.

Neptune
Michael Cammarata has been appointed chief executive officer at Neptune Wellness Solutions Inc. Cammarata is co-founder and previous chief executive officer of Schmidt’s Naturals, now a division of Unilever. He is also the founder of Random Occurrence.

Lyra Therapeutics
Laura M. Edgerly-Pflug has been named senior vice president of technical operations at Lyra Therapeutics. Edgerly-Pflug was most recently vice president of technical operations at Adgero Biopharmaceuticals Holdings.

Progenics
Progenics Pharmaceuticals has announced the appointment of Huw Jones as vice president, commercial. Jones was previously vice president of marketing and sales at Advanced Accelerator Applications.

Sunesis Pharmaceuticals
Sunesis Pharmaceuticals has announced two key promotions. Judy Fox has been named chief scientific officer and executive vice president for research & development; Parvinder Hyare has been appointed senior vice president, commercial. Fox was previously chief scientific officer and senior vice president; Par was previously vice president of global oncology operations.

Health Enterprise Partners
Health Enterprise Partners has announced the promotion of Elizabeth Colonna to vice president. Jessie Laurash has been named senior associate. Colonna was promoted from the position of senior associate with the company. Laurash most recently served as director of operations for MediQuire.

Anika
Anika Therapeutics has named James Looper to the newly created position of executive vice president of business development and strategic planning. Looper most recently served as chief corporate development officer at Lupin Pharmaceuticals.

EIP Pharma
Noel Donnelly has been appointed chief financial officer at EIP Pharma. Donnelly was most recently vice president of R&D business operations at Shire.

Skyhawk
Tai Wong has been named vice president of oncology biology at Skyhawk Therapeutics. Wong was most recently vice president of biology at Peloton Therapeutics.

Sheppard Pratt Health System
Todd Peters has been named vice president and chief medical officer at Sheppard Pratt Health System. Peters joined Sheppard Pratt in 2018 and served as its medical director of child and adolescent services and chief medical information officer.
FDA Recommends Endpoint for Hormone Analogs for Prostate Cancer

Testosterone level should be used as a surrogate endpoint in phase 3 trials of gonadotropin-releasing hormone (GnRH) analogs for treating advanced prostate cancer, the FDA says in a new draft guidance.

Sponsors should conduct single-arm trials that measure attainment and maintenance of castrate testosterone (T) levels, according to the draft guidance released last week. Trials should look at T levels maintained until the end of a dosing interval as well as immediately after later doses — not the first dose — of the study drug.

“To demonstrate these effects of the study drug on T levels, the treatment period should be at least twice as long as the dosing interval,” the agency advises. Products that act over shorter periods, such as one month, should have treatment periods extending over three to four dosing intervals.

Trial participants should have normal, age-adjusted T levels and metastatic disease in order to produce a more accurate safety profile of the intended population, the FDA says. It recommends documenting information about patients’ prostate cancer history, including the diagnosis date, current stage, prior therapies and the extent of metastatic disease at baseline.

Any indications besides treating advanced prostate cancer should be discussed with the agency before a sponsor begins a trial, the draft guidance says. Randomized designs for supporting efficacy and/or safety among GnRH analogs also should be discussed with the agency.

The draft guidance also provides recommendations for dose selection; trial procedures and timing of assessments; pharmacokinetics and pharmacodynamics; statistical suggestions and labeling considerations.

Read the guidance here: https://bit.ly/32zoyVU.

Heart Failure Trial Uses Biosensors to Gauge Patient-Centric Endpoints

A joint clinical study of patients with heart failure is using wearable biosensors to evaluate the viability and significance of patient-centric endpoints such as physical function and quality of life.

The multicenter study is being conducted by the Mayo Clinic and Yale University with assistance from the FDA in what is called a CERSI (Center of Excellence in Regulatory Science and Innovation), a collaboration between the agency and academic institutions.

The study follows a draft guidance the FDA released in June that would allow endpoints based on a treatment’s effect on patient-reported symptoms and experiences even if the treatment has no favorable effect on survival or risk of hospitalization (CenterWatch Weekly, July 1, 2019).

Researchers will use two different mobile devices to monitor discharged heart failure patients for 60 days, then analyze the data to measure the correlation between patient-reported outcomes and clinical endpoints, such as lab tests and physical examinations.

MHRA Issues Survey on Patient Engagement

The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) is seeking public feedback on how the agency involves patients in its work, including in clinical trials.

The goal is to find out how patients would like the MHRA to communicate with them and how patients would prefer to communicate with the MHRA to raise concerns.

“We want to adopt a more systematic approach to listening to and involving patients — ensuring that the patient voice is heard when safety issues, concerning medicines or medical devices, are identified and in the licensing of new medicines,” the agency says. MHRA’s “consultation” survey will be open until Oct. 7.


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Risk-Based Monitoring
continued from page 1

RBM as both a whole system and as part of an overall quality-by-design approach to clinical trial development and conduct. He outlined a three-stage approach to developing an RBM plan:
- Risk assessment for each discrete clinical trial;
- An appropriate and well-articulated study protocol that considers the identified risks; and
- An RBM plan that focuses on the highest study-specific risks.

Monitoring activities should focus on processes and procedures deemed most critical for protection of trial subjects and ensuring data integrity, Burrow said.

Most EU regulators have adopted risk-based quality standards and encourage RBM, said EMA scientific administrator Camelia Mihaescu. Aside from minor language differences, the EMA approach under EU regulation 536/2014 is very similar to the FDA’s. The EMA, like the FDA, encourages sponsors to position their RBM strategy within the broader quality concept, Mihaescu said.

One area that has proven confusing to sponsors is how centralized or remote monitoring should relate to the more traditional on-site monitoring. SDR and SDV, for instance, traditionally have been conducted via on-site visits, and it is unclear whether a sampling approach, which could be conducted under a more centralized monitoring scheme, would be acceptable for these activities.

Nicole Stansbury, vice president of global centralized monitoring at CRO Syneos Health Clinical Solutions noted that SDR and SDV have been combined with medical reviews over the years, but the items have not been tightly connected. The FDA could help drug sponsors by providing clearer guidance on how to achieve balance.

On-site monitoring likely will always have a role, Burrow added, but RBM strategies will need to involve greater use of centralized and remote tools, as well as various analytical tools to identify trends, missing or inconsistent data, variable data or outliers, protocol deviations and systemic errors. The idea is that RBM can better target risks to the most critical data elements and procedures of a trial, including SDV, SDR and evaluation of study conduct.

Sampling alone does not qualify as an RBM plan, Burrow cautioned. Sampling can be an important part of RBM, but must be included as part of a broader risk mitigation system.

Another key factor is change management. RBM is not a “set it and forget it” process, Burrow said. Because risk is complex and can change as a study progresses, companies must not consider RBM as a single risk assessment, but a continuous improvement concept.

And regulators, sponsors, CROs and sites all agree that companies cannot take a blanket monitoring approach to all studies regardless of design and risk factors. RBM must be tailored to match the specific risks of each individual study.

The FDA issued draft guidance, A Risk-Based Approach to Monitoring of Clinical Investigations — Questions and Answers, on March 19 and is currently reviewing comments on the guidance. There is no date set to make the draft guidance final.


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—David Burrow, director, CDER Office of Scientific Investigations
Financial Audits

continued from page 1

CTAs, 40 different budgets, 40 different payment terms," Russell said.

To explain the value of a financial audit, Russell talked about a site he worked with that had 600 open studies. Out of the 600 studies Russell audited 12. “What we found was a little over $75,000 was not even invoiced. And there was $31,000 that was invoiced but it wasn’t collected,” he said.

“So there was a total of $106,000 that was owed to the sites from those 12 studies. So it averages about $8,852 per study that is owed,” he said.

A second site had 250 studies and he chose only five studies to audit. “A little over $102,000 was not invoiced and nearly $34,000 was invoiced but not collected,” he said. “This averaged actually $27,174 per study,” he said.

“Don’t wait too long after the closeout visit to complete your final reconciliation. I’ve seen a lot of sites lose a lot of money because six months after the closeout visit they realize, oh, there’s $30,000 worth of unpaid invoices that they didn’t get to us,” Russell said.

Russell has some dos and don’ts:

Do:
- Conduct routine financial audits;
- Understand the payment terms for your studies;
- Maintain a reconciliation log to tie out all payments;
- Assure you are keeping up with all invoiceable items.

Don’t:
- Assume your CTMS will accurately track your receivables;
- Entrust the receivables management process to a study coordinator;
- Assume that the sponsor/CRO will pay you correctly;
- Presume that if you send an invoice you will be paid;
- Wait too long after your close-out visit to complete the final reconciliation.

“Sponsors and CROs are typically not going to remind you to send them invoices or to request the funds that you’ve already agreed to.”

—David Russell, director of site strategy, PFS Clinical

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- The increased use of centralized institutional review boards (IRBs)

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<td>tarisbio.com</td>
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<td>IDE196</td>
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<td>neflamapimod</td>
<td>Huntington's disease</td>
<td>Phase 2 trial initiated enrolling 16 subjects at a site in Cambridge UK</td>
<td>eippharma.com</td>
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<td>Cara Therapeutics, Inc.</td>
<td>Oral KORSUVA (CR845/difelikefalin)</td>
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<td>Dilafor AB</td>
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<td>NeuroRx, Inc.</td>
<td>NRX-101</td>
<td>Severe Bipolar Depression and Acute Suicidal Ideation and Behavior (ASIB)</td>
<td>Phase 2b/3 trial initiated enrolling 140 subjects with Severe Bipolar Depression and ASIB who are stabilized following a single IV infusion of ketamine JPS Health Network in Fort Worth, Texas</td>
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<td>Mirum Pharmaceuticals</td>
<td>maralixibat</td>
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<td>CSTone Pharmaceuticals</td>
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<td>selinexor in combination with dexamethasone</td>
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<td>ConTIPI Medical, Ltd.</td>
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<td>Azurity Pharmaceuticals</td>
<td>Katerzia (amlodipine) Oral Suspension, 1 mg/mL</td>
<td>hypertension (high blood pressure) in adults and pediatric patients six years of age and older and coronary artery disease in adults</td>
<td>Approval granted by the FDA</td>
<td>azurity.com</td>
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