Complex Data Need Simplified Trials, Expert Argues

By Bill Myers

Clinical trials professionals will have to be laser-focused as emerging technology tempts them into a fool’s paradise of big data, a top industry analyst tells CenterWatch.

Machine learning, artificial intelligence and even consumer electronic apps are offering troves of data that would have been unimaginable even a couple of decades ago, says Ken Getz, an associate professor at the Tufts Center for the Study of Drug Development.

But if sponsors, sites and investigators aren’t careful, they can lose control of their studies and see knowledge dissolve in information.

“It is a paradox of our age — right at the time when our complexity has risen so that it’s having a negative impact on our performance, we’re at the same point where we can collect so much information on every aspect of our trials,” Getz said after presenting at the inaugural Metrics Champion Consortium conference last week. “It’s very tempting, isn’t it, to just collect more data? We’ll just let the machine do the thinking for us. And that’s also dangerous.”

Data and information technology have already made trials incredibly complex, he says. According to a Tufts analysis, the average trial has seen the total number of endpoints rise 86 percent since the beginning of the century. The number of eligibility criteria has risen by 61 percent, the total

FDA Trials Inspection Algorithm: Be Ready

By Bill Myers

The clinical trials industry is just coming to grips with a new FDA approach to inspections that uses advanced computer algorithms to flag trials for risk.

The agency has spent the past few years preparing for centralized trial inspections and issued a draft guidance on them in February but it’s still relatively early in the process, says Cerdi Beltre, senior vice president for institutional services at the WIRB-Copernicus Group. Until trial professionals get a better sense of how the algorithm works, they should do some self-auditing, she adds.

Some boxes to check, she says: “How are they ensuring all the sites are compliant? What resources are available? What high-level checklist can they have to prepare for that?”

Beltre’s advice comes on the heels of a presentation by Jean Mulinde, senior policy advisor at CDER’s clinical compliance evaluation division, laying out how the FDA’s “decision tree” algorithm helps the agency determine which trials to inspect.

Mulinde has been briefing sites and sponsors every chance she gets in recent months — including at last week’s Metrics Championship Consortium conference — to help them prepare. But Beltre said it was still eye-opening to hear a top regulator acknowledge that inspections are driven in part by a computer code.

The process is complex — and the FDA is

see Complex Data on page 4

see Inspection Algorithm on page 5
FDA Proposes Informed Consent Waivers for Some Clinical Trials

Researchers in low-risk clinical trials could experiment on patients without obtaining informed consent if they meet at least four conditions, the FDA proposed last week in a new rulemaking notice.

The agency will grant waivers if researchers can prove:

- A trial “involves no more than minimal risk” to humans;
- The waiver won’t negatively affect patients’ health or rights;
- A trial can’t “practically be carried out” unless a waiver is granted; and
- Patients are given study details and findings after a trial wraps up.

The proposed rules firm up a 2017 guidance that laid out the same conditions for informed consent waivers and conform to the Common Rule.

David Borasky, vice president of IRB compliance at the WIRB-Copernicus Group, welcomed the draft guidance, noting the new rules will help sponsors embrace modern technologies for clinical trials. He added that many IRBs are already using waivers under last year’s guidance.

“As the FDA continues to express an interest in having sponsors utilize retrospective real-world evidence to inform the regulation of drugs and devices, there will be a greater and greater need for mechanisms to allow activities like retrospective chart reviews — which can involve human subject research — to go forward under a waiver of informed consent,” Borasky tells CenterWatch.

But he questioned why the FDA pegged its new rules to the old Common Rule. A revised Common Rule is scheduled to take effect early next year and offer another reason for informed consent waivers.

“It is not clear from the proposal why the FDA would harmonize to a rule that will be out of date within a few months,” Borasky says.

“The FDA has asked for comments on this, and I suspect that they will receive a lot of comments encouraging complete harmonization with the revised rule,” he adds. “Harmonizing to an outdated rule does not make sense in the big picture, even if the regulated community lacks experience implementing the new waiver criterion.”

Read the agency’s rulemaking notice here: https://bit.ly/2OSPGEq.

FDA Considers Endpoints for Rare, Deadly Prostate Cancer

The FDA has issued new draft guidance for clinical trials aimed at a rare but aggressive form of prostate cancer.

A very small percentage of men develop nonmetastatic, castration-resistant prostate cancer, defined by rising levels of prostate-specific antigens even after testosterone levels have been reduced. The disease can take years to run its course, which has made it difficult for sponsors to use overall survival rates — a common measure in cancer trials — as an endpoint.

The major concern is that by the time related tumors crop up, the deadly disease progresses rapidly. For years, sponsors, researchers and other experts have urged the FDA to consider metastasis-free survival a primary endpoint for trials aimed at the rare cancer. The agency now says it’s open to doing so but wants to be sure researchers carefully map out their plans.

Toward that end, it recommends sponsors:

- Define what they mean by “metastasis-free survival” before the trial starts;
- Consider grouping patients by the type of therapy (radiation, surgery) they had (or didn’t have) before being diagnosed with this cancer;
- Draw up procedures to account for patients who withdraw from trials because of concerns over rising prostate levels;
- Be clear about the kind of imaging they’ll use to test for the disease and its progression. For instance, some patients with nonmetastatic, castration-resistant prostate cancer have enlarged pelvic lymph nodes. In that case, sponsors should make clear how large nodes should be for a patient to be included in the trials; and
- Put together procedures “to minimize missing data.”

The draft guidance, issued last week, also suggests that sponsors avoid interim efficacy analyses — “because it may lead to over- or underestimation” of a treatment’s impact.

Even though overall survival probably won’t count as a primary endpoint, the FDA urges sponsors to conduct a formal interim analysis of overall survival, and “expects continued follow-up for final” overall survival even after a trial concludes.

Read the FDA’s draft guidance here: https://bit.ly/2zbjnyG.

App Gets to Heart of the Matter

A smart phone app appears to be just as effective at diagnosing severe heart attacks as traditional electrocardiograms.

```
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> Consider grouping patients by the type of therapy (radiation, surgery) they had (or didn’t have) before being diagnosed with this cancer;
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A smart phone app appears to be just as effective at diagnosing severe heart attacks as traditional electrocardiograms.
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Researchers enrolled 204 patients in clinical trials at five sites to test the AliveCor app. Patients were connected to AliveCor, which is administered by a smart phone and has two wires, and two traditional, 12-lead ECGs.

“We found the app helped us diagnose heart attacks very effectively—and it didn’t indicate the presence of a heart attack when one wasn’t occurring,” lead researcher J. Brent Muhlestein of the Intermountain Medical Center Heart Institute in Salt Lake City, Utah, said in announcing his team’s findings.

Stanford researchers are currently testing a heart monitor offered by Apple Watch on some 400,000 patients — the largest clinical trial of its kind.

**Lab Owner Nabbed in Trial Scam**

Federal officials have indicted a laboratory owner on charges that he bilked drug sponsors in an opioid clinical trial.

Sami Anwar, of Richland, Wash., and two of his companies — Mid Columbia Research and Zain Research — face 47 separate felony counts, including wire and mail fraud, fraudulently obtaining controlled substances and lying to federal agents, in what authorities allege was a scheme to pocket fees for a phony clinical trial supposedly trying to find non-opioid pain treatments.

Anwar and his staff are accused of enrolling ineligible participants in the trial, forging doctors’ signatures and faking records to make it seem like patients were participating in the trial and taking the experimental drug.

The sham trial netted in excess of $250,000 from the unnamed drug sponsor, federal authorities allege in charging documents.

Anwar has denied wrongdoing. He’s facing up to 20 years in prison and $250,000 in fines, federal authorities say.

**EMA Issues Guidance on Safety Monitoring for Pediatric Drugs**

The European Medicines Agency (EMA) has released new guidance calling for sponsors of pediatric drugs to step up monitoring of adverse effects.

It’s important to track effects of medicine in pediatric patients because clinical trials are usually limited in their size and duration, and adverse reactions can differ a lot more in kids than in adults, the EMA says. The final guideline — chapter IV of the agency’s good pharmacovigilance practices (GVP) — applies to approved drugs with pediatric indications and drugs used off-label for treating children ages 2 to 11.

The EMA notes that growth and maturation factors in pediatric patients — such as immature organ systems, physiological changes in growth and development, and changes in body mass and composition — mean that they respond substantially differently than adults to adverse events. Because of this, considerations for long-term follow up should carefully weigh these factors.

Findings from adult clinical trials should be used to identify potential risks, characterize the safety profile and determine tools for reducing risk in the pediatric population. But sponsors should also consider the effect of meds on bone and cartilage during active growth; potential adverse reactions from different exposure to metabolites compared to adults; and the long-term effect on developing reproductive and neurodevelopmental systems, the guidance says.

The EMA recommends info sponsors should include in adverse reports, too, such as dosage data, indication or intended use, and the patient’s accurate age, weight and height/length at the time of reaction.

Read the full guidance here: https://bit.ly/2zPqH2k.

**FDA Panel Weighs In on Trials of Novel Non-Opioids**

An FDA advisory panel nixed clinical trials for opioid substitutes without active comparators and a looser definition of “opioid-sparing.”

The Anesthetic and Analgesic Drug Products Advisory Committee voted 12-1 that trials for novel non-opioids should involve an active comparator design so the FDA can determine if tested drugs provide a significant clinical benefit over currently available meds.

“I would want to see what’s out there in the market,” said patient representative James O’Brien, president and CEO of the National Scoliosis Foundation, endorsing trials conducted against active comparators.

The sole “yes” vote, Mary Ellen McCann of Harvard Medical School, said she wouldn’t necessarily design a trial without an active comparator but could see such a study gleaning useful information.

The committee, by an 11-1 margin, also rejected defining a drug as “opioid-sparing” simply because it leads to a decrease in opioid use.

Members expressed doubt the term was appropriate as a broad claim without context for the drug’s benefit-risk profile or consideration for the population, setting and variability in practice — and worried it could confuse consumers. They said seeking the broader opioid-sparing definition might introduce perverse incentives into clinical trial design such as withholding standard approaches to analgesia.

“I don’t think any line of evidence would support a broad labeling of a drug as opioid-sparing,” said temporary member James Floyd, an assistant professor of medicine and epidemiology at the University of Washington. Abby Shoben, an associate professor in the division of biostatistics at the Ohio State University’s College of Public Health, also voted “no,” saying she would prefer a definition incorporating more meaningful clinical outcomes, such as reduction in the number of pills dispenses.

For the purposes of the advisory committee, the FDA defined opioid-sparing drugs as drugs or combinations of drugs that contain no opioids that, when used with opioid analgesics, reduce opioid analgesic use. Opioid-sparing drugs are distinct from novel non-opioid drugs, which are meds or med combos that can be substituted outright for an opioid analgesic.
number of procedures performed in a trial by 70 percent and the number of countries involved in a trial has risen 100 percent.

It’s no coincidence, Getz argues, that drug development costs have risen as dramatically as trial complexity. The average price tag for developing a drug was around $1 billion in 2003, according to Tufts data; a decade later, the average tab had nearly tripled.

Perhaps most troubling is that barely a quarter of those costs have been directly tied to development, Getz says, noting that almost a fifth of them stem from time wasted sifting through irrelevant data.

“‘It’s very tempting, isn’t it, to just collect more data?’”

—Ken Getz, associate professor, Tufts Center for the Study of Drug Development

The amount of “non-core” data has risen by 78 percent since the early 2000s, Tufts reports.

“It’s all around optimizing and utilizing the information really wisely and effectively,” Getz says. “In this age where there’s just this explosion of data, how do we use it really intelligently?”

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### Complex Data

continued from page 1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Total Number of Endpoints</td>
<td>7</td>
<td>13</td>
<td>86%</td>
</tr>
<tr>
<td>Total Number of Eligibility Criteria</td>
<td>31</td>
<td>50</td>
<td>61%</td>
</tr>
<tr>
<td>Total Number of Distinct Procedures</td>
<td>22</td>
<td>35</td>
<td>59%</td>
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<tr>
<td>Total Number of Procedures Performed</td>
<td>110</td>
<td>187</td>
<td>70%</td>
</tr>
<tr>
<td>Total Number of Planned Volunteer Visits</td>
<td>12</td>
<td>15</td>
<td>25%</td>
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<tr>
<td>Proportion of Data ‘Non-Core’</td>
<td>18%</td>
<td>32%</td>
<td>78%</td>
</tr>
<tr>
<td>Number of Investigative Sites</td>
<td>40</td>
<td>65</td>
<td>63%</td>
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<tr>
<td>Number of Countries</td>
<td>5</td>
<td>10</td>
<td>100%</td>
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<tr>
<td>Number of Patients Randomized</td>
<td>729</td>
<td>597</td>
<td>-18%</td>
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<tr>
<td>Direct Cost Per Procedure per Patient per Visit</td>
<td>$728</td>
<td>$978</td>
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<tr>
<td>Total Data Points Collected</td>
<td>494,236</td>
<td>929,203</td>
<td>88%</td>
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<tr>
<td>Number of Data Collection Applications Used</td>
<td>2</td>
<td>6</td>
<td>200%</td>
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Source: EvaluatePharma; William Blair & Wells Fargo Securities; Tufts CSDD

### High Annual and Capitalized Costs

#### Annual Global Spending on Pharma R&D

<table>
<thead>
<tr>
<th>Year</th>
<th>$US Billions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>$33.9</td>
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<tr>
<td>2000</td>
<td>$54.6</td>
</tr>
<tr>
<td>2005</td>
<td>$94.2</td>
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<tr>
<td>2010</td>
<td>$127.4</td>
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<tr>
<td>2015</td>
<td>$142.2</td>
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#### Capitalized Cost to Develop a Successful Drug

- 26% Direct Costs
- 18% Time-Based
- 56% Cost of Failure

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<thead>
<tr>
<th>Year</th>
<th>$US Millions (2013 dollars)</th>
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<tbody>
<tr>
<td>2003</td>
<td>$1,044</td>
</tr>
<tr>
<td>2013</td>
<td>$2,558</td>
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Source: Tufts CSDD

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**Clinical Trial Financial Management**

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Inspection Algorithm
continued from page 1

keeping some of its inputs close to the vest — but the essence of it is that the agency is assigning weighted values to certain risks, such as a trial having a new investigator on staff (see chart below). It then runs the different values through a three-part calculation to come up with a risk score. Trials with higher risk scores are more likely to be inspected. It’ll be interesting to see how, or whether, the automation changes the nature of the agency’s inspections regime, Beltre says.

“How is this different than the old way of selecting sites for inspection? Does the industry need to prepare or do anything different than before? What changes shall we anticipate for sponsors, CROs and sites?” she wonders, adding some answers may not come until there’s more data available.

Linda Sullivan, MCC’s co-founder and president, says shedding light on the process actually reassured trials professionals that the FDA is still focusing on the broader context of trials even though it’s using advanced statistics to inform its inspections.

“There’s been a lot of anxiety around inspections,” Sullivan says. Melinde “calmed a lot of fears. While we may see things in the numbers, we do spend the time to try to understand the context.”

Trials professionals should do some self-auditing until they get a better sense of how the algorithm works.

—Cerdi Beltre, senior vice president for institutional service, WIRB-Copernicus Group

Inputted Data Processed via Decision Tree Algorithm

<table>
<thead>
<tr>
<th>Attribute Raw Values</th>
<th>Risk Functions applied to Attribute Values</th>
<th>Hierarchical Weighting Schema applied</th>
<th>Final Risk Score for each site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Attribute Raw Values</td>
<td>2 Risk Functions applied to Attribute Values</td>
<td>3 Hierarchical Weighting Schema applied</td>
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</tbody>
</table>

Source: FDA; Maintaining Quality in Clinical Research – Optimizing Planning and Oversight Activities

A crash course in what you should and shouldn’t say in a CTA

Clinical Trial Agreements
A Guide to Key Words and Phrases

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## Drug & Device Pipeline News

For news on trial results, FDA approvals and drugs in development, Join the LinkedIn Drug Research Updates group!

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Device</th>
<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
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<tr>
<td>Stallergenes Greer</td>
<td>Oralair®, an allergy immunotherapy sublingual tablet</td>
<td>Grass pollen-induced allergic rhinitis</td>
<td>Received FDA approval for the extension of the indication to treat patients ages five to nine</td>
<td>stallergenesgreer.com</td>
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<tr>
<td>REGENXBIO</td>
<td>RGX-181, a one-time treatment candidate</td>
<td>Late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease, one of the most common forms of Batten disease</td>
<td>Granted Orphan Drug Designation by the FDA</td>
<td>regenxbio.com</td>
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<td>Eli Lilly and Company</td>
<td>Lasmiditan</td>
<td>Migraine with or without aura in adults</td>
<td>Submitted a New Drug Application (NDA) to the FDA</td>
<td>lilly.com</td>
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<tr>
<td>Eli Lilly and Company</td>
<td>Emgality</td>
<td>Episodic cluster headache</td>
<td>Granted Breakthrough Therapy Designation by the FDA</td>
<td>lilly.com</td>
</tr>
<tr>
<td>Lumendi</td>
<td>DiLumen™ EIP</td>
<td>Easier dissection and resection of polyps without the need for surgical intervention</td>
<td>Received 510(k) clearance from the FDA</td>
<td>lumendi.com</td>
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<tr>
<td>Theravance Biopharma, Inc. and Mylan N.V.</td>
<td>YUPELRI™ (revefenacin), once-daily, nebulized bronchodilator</td>
<td>COPD</td>
<td>Granted approval by the FDA</td>
<td>theravance.com mylan.com</td>
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<tr>
<td>Biohaven Pharmaceutical Holding Company Ltd</td>
<td>Rimegepant, oral calcitonin gene-related peptide (CGRP) receptor antagonist</td>
<td>Migraine</td>
<td>Enrolled first patient in Phase III clinical trial</td>
<td>biohavenpharma.com</td>
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<td>AbbVie</td>
<td>Mavyret (glecaprevir/pibrentasvir)</td>
<td>Hepatitis C (HCV)</td>
<td>Results from Phase IIIb EXPEDITION-8 trial: patients receiving the drug for 8 weeks with genotype 1, 2, 4, 5 and 6 had a 100-percent sustained virologic response 12 weeks after treatment</td>
<td>abbvie.com</td>
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<td>Merck</td>
<td>KEYTRUDA® (pembrolizumab)</td>
<td>Advanced or metastatic esophageal or esophagogastric junction carcinoma in patients whose tumors expressed PD-L1</td>
<td>Significantly improved Overall Survival (OS) compared to chemotherapy in Phase III KEYNOTE-181 clinical trial</td>
<td>merck.com</td>
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<td>AbbVie</td>
<td>Elagolix, in combination with add-back therapy</td>
<td>Heavy menstrual bleeding associated with uterine fibroids</td>
<td>Achieved statistically significant reduction in two replicate pivotal Phase III clinical trials</td>
<td>abbvie.com</td>
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<td>Calliditas Therapeutics</td>
<td>NEFIGARD</td>
<td>IgA nephropathy (IgAN)</td>
<td>First patient enrolled in pivotal Phase III clinical trial</td>
<td>calliditas.com</td>
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<td>Palvella Therapeutics, Inc.</td>
<td>PTX-022 (novel, high-strength rapamycin topical formulation)</td>
<td>Pachyonychia congenita (PC)</td>
<td>Granted Fast Track Designation by the FDA</td>
<td>palvellatx.com</td>
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<td>TWi Biotechnology, Inc.</td>
<td>AC-201CR</td>
<td>Hemophilic arthropathy</td>
<td>Completed patient enrollment in Phase II clinical trial</td>
<td>twipharma.com</td>
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