Ahead on the Science, Behind on the Tech: Clinical Trials Wrestle with AI’s Emergence

By Bill Myers

Earlier this year, Swiss-based pharma giant Novartis began an ambitious transition that company leaders say will ultimately change it from a drug maker to a data management company.

With Nerve Live, a set of artificial intelligence platforms, Novartis has pushed itself to the leading edge of AI technology in clinical trials — incorporating machine learning and advanced data analytics not just into the company’s business units, but into its core operations, too.

“We certainly realized that on the patient side and on the operational side we were sitting on a huge wealth of data and we were under-utilizing the data,” says Luca Fi

Final Guidance, Hay Fever, Non-Allergic Rhinitis Trials

By Bill Myers

The FDA has issued new guidance for clinical trials testing drugs designed to treat hay fever as well as sniffles and other cold-like symptoms that aren’t caused by allergies.

In a pair of final guidances, released last week, the FDA urges drug sponsors to focus as much as possible on real-world settings when trying to determine ideal doses for proposed medicines. But hay fever, formally known as allergic rhinitis, is better known, so the agency says it’s taking a more precise approach to clinical trials.

Non-Allergic Rhinitis

Unlike hay fever, it’s harder to define and diagnose runny, stuffy noses that aren’t directly caused by allergies; typically, they can only be pinned down after allergies or other possible conditions (like the flu) have been ruled out. So the FDA stresses drug sponsors consider real-world conditions for their trials, from patient recruitment to dosing. They should also target the specific subtype of rhinitis — or symptoms — they hope to address, which may require them to run preliminary studies to narrow their scope.

Once they’re ready to go, the FDA says it will consider trial designs other than the traditional Phase I, II and III mold. For instance, the agency says that while it prefers sponsors to test under real-life conditions, it’s open to “alternative exposure models,” though the guidance doesn’t offer any specifics about other potential trial designs.

Drug & Device Pipeline News...6
Fifteen drugs and devices have entered a new trial phase this week.

Research Center Spotlight...8
Research center profiles.
FDA Tackles Device Uncertainty in Clinical Trials

The FDA may accept some uncertainty about the safety of a proposed medical device if sponsors carefully collect and report data after it hits the market, the agency says in new draft guidance.

The 21st Century Cures Act requires the FDA to fast-track approval for “breakthrough devices”—innovative gadgets that offer more effective treatment or diagnoses for life-threatening or debilitating diseases than apparent rivals or that don’t have any approved competitors so speeding them to market would be “in the best interest of patients.”

But fast-tracking breakthrough devices—or devices that target extremely rare diseases—may mean that regulators have to accept some unanswered safety questions.

Last week’s 22-page draft guidance is the FDA’s attempt to come to grips with that uncertainty.

“The aim,” Commissioner Scott Gottlieb said in a speech announcing release of the proposed guidelines, “is to support premarket decisions that are based on the totality of scientific evidence available at the time of a device’s market entry.”

Though couched in careful language, the draft suggests that regulators might be willing to exchange unanswered pre-approval questions for post-approval answers.

That means, for example, sponsors should expect strict post-market safety reporting deadlines based on real-world data. They may also have to agree to careful labeling outlining pending safety questions and to post-market review by an FDA advisory council, which could result in having marketing approval limited or yanked.

The new measure builds on final guidance the agency issued in 2016, laying out ways regulators would analyze the risk of new drugs and devices. That final guidance focused mostly on the potential harms caused by a proposed device; the new draft suggests that regulators might be willing to accept some uncertainty if sponsors can show “probable” patient benefits from early access to the device and if:

- A disease or disorder is so rare that gathering clinical data isn’t feasible;
- Bringing a device to market would allow sponsors and regulators to gather safety data; and
- Post-market remedies, such as warning labels, would likely to mitigate any harm.


Final Guidance, PBPK Analyses

The FDA last week released final guidance for drug sponsors on the content and formatting of physiologically-based pharmacokinetic (PBPK) analyses, including an expanded section on formatting and a simplified section on software.

The agency said any analysis should explain how the PBPK modeling and simulation address clinical, scientific and regulatory questions, adding that the “basis for any requests to waive the conduct of clinical studies should be discussed and well substantiated.”

If simulations are used to support specific dosing recommendations tested in future clinical trials or incorporated into prescription drug labeling, the proposed doses should be “discussed and justified within the totality of evidence, including the context of known exposure-response relationships and the level of confidence in the PBPK model for its intended uses,” the guidance states.

Sponsors should include the dosing regimen in their description of simulation conditions and, when applicable, the numerical methods used to solve differential equations.

When sponsors use library drug and system models within a specific software platform, they need to justify their use and also “identify and justify modifications made to the library models,” the agency said.


CRISPR, Vertex Launch Trial

A pair of Massachusetts biotech firms has begun recruiting for a clinical trial testing gene-editing techniques on patients who have a rare blood disease.

CRISPR Therapeutics and Vertex Pharmaceuticals last week began enrolling patients suffering from beta thalassemia, a disorder that cuts the number of oxygen-carrying red blood cells and can cause fatigue and even fatal anemia.

The Phase I/II trial hopes to recruit 30 patients to determine whether the CRISPR treatment CTX001 will reduce the amount of blood transfusions they need for at least six months.

The trial is scheduled to run through May 2022.

Trial Access for a Price?

A new U.S. startup, backed by funds from a Hong Kong billionaire, is charging cancer patients for the chance to link up to worldwide treatments and clinical trials.

The company, dubbed Driver, officially launched last week. It charges patients an initial entry fee of $3,000 and then $20 a month for access to about three dozen hospitals, clinics, research sites and other...
institutions in three countries. The monthly fee covers follow-up service during which Driver promises to monitor patients’ health and offer suggestions on further care.

The way it works: patients turn over their medical records to the company — and can even send tumor samples to Driver’s labs for analysis.

It offers access to 30 health centers in the U.S., four in mainland China and one in Singapore.

**FDA OKs Hemophilia A Treatment**

The FDA has approved Bayer’s Jivi as a preventative treatment for hemophilia A.

Jivi, the brand name for the treatment BAY94-9027, spent two years in a Phase II/III clinical trial, during which the IV treatment successfully stopped bleeding in patients for an average of nearly two years.

The trial enrolled 141 patients between 2012 and 2014 and split them into two groups: one that received the treatment as needed to stanch bleeding and the other given an infusion of the med as a preventive. In 2014, researchers reported that Jivi seemed effective as an on-demand response to bleeding, resolving 91 percent of severe bleedings with one or two treatments.

Now the trial results have shown it can help ward off bleeding, too.

Hemophilia A is a genetic disorder in which patients lack a protein that helps blood clot. It’s much more prevalent in boys than girls, occurring in about one in every 5,000 males born, according to the National Hemophilia Foundation.

**New HIV Drugs Approved**

Merck has won FDA approval for two oral drugs designed to treat the most common strain of HIV.

Delstrigo is a once-a-day tablet that contains three different anti-retrovirals. The agency approved the drug with a black box warning because of concerns that it may aggravate hepatitis B infections.

Pifeltro is also an oral medicine that’s designed to be taken along with other anti-retrovirals. In Delstrigo’s trial, researchers recruited 728 HIV-positive patients who had never taken anti-retrovirals and randomly gave them either Delstrigo or another combination therapy daily. At 48 weeks, Delstrigo had suppressed viral loads in 84 percent of the patients, compared to 81 percent of patients taking the other drug combo.

For the Pifeltro trial, researchers recruited another 766 HIV-positive patients who had never taken any other anti-retroviral. They, too, were randomly given daily doses of Pifeltro or another anti-retroviral. After 48 weeks, nearly 84 percent of Pifeltro patients were testing negative for HIV, compared to about 80 percent of participants taking the other treatment.

More than 70 million people worldwide have been infected with HIV and some 35 million have died since the AIDS epidemic began, according to WHO.

---

**Medical Device Guidance**

**SOP for Good Clinical Practice by Sponsors of Medical Device Clinical Trials** is the industry’s only medical device SOP available that reflects best practices while addressing FDA Guidance documents and current device regulations to minimize your organization’s regulatory exposure and comply with industry standards.

Highlights include:

- **✓ Succinct overview of the clinical investigational process**
- **✓ CRO/vendor management guidelines**
- **✓ Key elements from ISO 14155**
- **✓ Guidance on risk-based monitoring and technology implementation**
- **✓ Important medical device development steps**

VISIT STORE.CENTERWATCH.COM

TO ORDER store.centerwatch.com CONTACT SALES sales@centerwatch.com (617) 948-5100
AI’s Emergence
continued from page 1

range of data — the kind of disease or drug they’d like to study, say, or the countries they believe may have promising research — and their computer will spit out recommendations for sites likely to meet enrollment needs or that offer quality records or info researchers may need.

When the company ran simulations as it prepared the Optimizer for launch, it estimated it could improve its patient enrollment by 15 percent.

The Optimizer also brings back near-real time data on trials that are already underway and flags potential problems — like that a site isn’t hitting early recruiting goals or has quality issues.

Finelli declined to discuss how much Novartis has budgeted for Nerve Live but acknowledges he has devoted a lot of time and effort to it. (The project has been in the works since 2015.) The biggest obstacle has been to make sure that the data collected and processed is “clean” so the machine can read it clearly.

That’s no easy task given that Novartis has amassed mountains of records during its decades of business that were mostly written for individual trials not predictive analytics and, so, weren’t always uniform.

Finelli says it’s still too early to say whether Nerve Live will deliver the results the company hopes for — it will take another year or so to gather the kind of data Novartis needs to measure outcomes — but early signs are promising. When Finelli’s team first began deploying the Footprint Optimizer, for instance, about 200 employees were using it regularly. That has ballooned to 2,000 — about one-fifth of the company’s drug development staff.

As slow as that progress may seem, Novartis is light years ahead of the clinical trial industry on this front.

“The industry has nowhere even scratched the surface at adopting AI,” says April Mulroney, WCG Clinical’s chief data officer. “We are so far ahead on advance-

ment in science — we’re doing some really cool stuff, scientifically, in clinical trials — but we’re so far behind on using advanced technologies.”

The Tufts Center for the Study of Drug Development estimates that, all in, it costs around $2.6 billion to bring a new drug to market. AI offers the chance to dramatically trim and cut any waste out of the process, Mulroney says.

So why are most in the industry so slow to embrace it?

“We need to change the way we view data,” Mulroney says, noting that most executives see data as raw information, when in fact it’s a valuable asset.

That’s roughly the bet that Novartis is making.

Earlier this year, the company appointed Bertrand Bodsen — a former executive who changed Argos from a traditional catalogue company into the UK’s third-largest online retailer — as its first-ever chief digital officer. He reports directly to Novartis CEO Vasant Narasimhan.

For Finelli, it’s a sign of Novartis’ commitment to reinventing itself.

“Our ambition,” he says, “is to bring Big Data to every line item in drug development.”

“The industry has nowhere even scratched the surface at adopting AI.”

— April Mulroney, chief data officer, WCG Clinical

The CRC’s Guide to Coordinating Clinical Research

The CRC’s Guide is the most comprehensive, easy-to-read training guide for novice and experienced clinical research coordinators.

- Comprehensive review of the CRC role and responsibilities
- Understanding regulations, GCPs and the IRB role
- Preparing for and closing a clinical study
- Strategies on patient recruitment, engagement and retention
- And much more!

ORDER TODAY 🚚 store.centerwatch.com ☎️ sales@centerwatch.com 📞 (617) 948-5100
Features

Final Guidance
continued from page 1

The guidance notes that sponsors should carefully monitor patients’ responses to scents and other irritants, especially in trials for potential treatments for vasomotor rhinitis — the most common form of non-allergic rhinitis — because some drug formulas have been known to change sensitivities to smells.

Hay Fever
Generally, the FDA says that it would prefer at least two Phase III clinical trials for drugs aimed at treating seasonal and perennial nasal allergies, but that it would consider a single trial as long as it’s “adequate and well-controlled” and “demonstrates the safety and effectiveness of the drug.”

It urges sponsors testing a proposed seasonal allergy elixir to work quickly when randomizing patients in a trial “because this generally reduces variability in allergen exposure.” For drugs treating perennial allergies, it’s still best to test efficacy in the off-season to minimize the risk that seasonal allergies may pop up during trials.

As far as recruiting goes, the guidance says that sponsors should enroll seasonal-allergy sufferers with at least a two-year history of hay fever — and that participants shouldn’t start an immunotherapy or change their regular treatment or dose within at least a month of the trial. Patients with acute or chronic sinusitis, chronic asthma and/or a history of using corticosteroids, leukotriene modifiers (asthma drugs like Singulair) or long-acting antihistamines should probably be excluded from trials, the FDA advises.

“We recommend that all key trials in the development program, including dose-ranging trials and confirmatory efficacy and safety trials, be conducted with the to-be-marketed product.”

—FDA Guidance

Safety, of course, is paramount, so sponsors should conduct routine lab tests at least twice on potential participants to check such things as liver and kidney function — once at the initial screening for a Phase III trial and again at the end of the trial. They should also keep an eye on volunteers’ heart health, performing an EKG “early in clinical development,” the FDA recommends.

Corticosteroids
A drug’s safety profile should include at least six months of data from 300 or more trial participants and a year or more of data from 100-plus patients, with the overall patient database including at least 1,500 patients. An undefined “sufficient number” of volunteers should be given the maximum dose of the proposed drug during a clinical trial. For children, sponsors should add an additional three months’ worth of data for intranasal products and one additional month for those taken by mouth.

If sponsors are testing meds containing corticosteroids, they should screen adrenal function at least once before participants begin taking the candidate drug and at least six weeks after they start taking it, the guidance says. Sponsors should also be on the lookout for signs of cataracts and glaucoma, potential side effects of continued steroid use.

The FDA urges sponsors to proceed with caution if testing corticosteroids on kids — and perhaps skip oral prednisone trials in children. In any pediatric trials, the guidance recommends a six-week hypothalamic-pituitary-adrenal axis trial, a complex analysis of how glands are handling a new drug; it also encourages sponsors to get a pre-trial baseline measure to make sure proposed drugs aren’t stunting growth.

For topical meds, sponsors should give adult patients nasal exams — initially to establish baseline health and then to monitor potential side effects on the area being treated. The FDA reminds sponsors that they consider a topical drug’s delivery system as part of its review, meaning the whole product is being evaluated as a hybrid drug/device trial.

“Therefore, we recommend that all key trials in the development program, including dose-ranging trials and confirmatory efficacy and safety trials, be conducted with the to-be-marketed product,” the guidance says. “Depending on the nature and extent of the changes, the altered product may be viewed as a new product, necessitating a separate development program with efficacy and safety trials.”


Service providers—showcase your expertise with an Industry Provider Profile page.

Reach Sponsors, CROs, and research sites with a profile outlining your unique products and services
Profiles are selected for a monthly feature in our CWWeekly publication to promote your organization and nurture new business leads within the industry

POST AN INDUSTRY PROVIDER PROFILE Contact sales to get started: ☑ sales@centerwatch.com ☑ (617) 948-5100
Celebrating 50 Years of Pioneering, Together.

It isn’t in our nature to seek the limelight or to sing our own praises. But when you turn 50, well, that’s something pretty special. We don’t want to celebrate alone though, because we know the real power comes from pioneering together. To all of those who share our passion for protecting people and are inspired by science and medical discovery, a heartfelt thank you for joining us on our first 50 years of pioneering together!

www.wcgirb.com/50
## Drug & Device Pipeline News

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug/Device</th>
<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen</td>
<td>Esketamine nasal spray</td>
<td>Treatment-resistant depression in adults</td>
<td>Submitted a new drug application to the FDA</td>
<td>janssen.com</td>
</tr>
<tr>
<td>EpicGenetics</td>
<td>BCG (an inexpensive generic vaccine to prevent tuberculosis)</td>
<td>Fibromyalgia</td>
<td>Massachusetts General Hospital granted FDA approval for human trial</td>
<td>fmtest.com</td>
</tr>
<tr>
<td>ARMGO Pharma, Inc.</td>
<td>ARM210 (also known as S48168)</td>
<td>Ryanodine Receptor Type 1 Related Myopathies (RYR1-RM)</td>
<td>Granted Orphan Drug Designation by the FDA</td>
<td>armgo.com</td>
</tr>
<tr>
<td>Lysogene</td>
<td>LYS-SAF302</td>
<td>Mucopolysaccharidosis Type IIIA (MPS IIIA)</td>
<td>Granted Investigational New Drug (IND) clearance by FDA for Phase II-III (AAVance) trial in U.S.</td>
<td>lysogene.com/en</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Oral Janus kinase 3 (JAK3) inhibitor PF-06651600</td>
<td>Alopecia areata, a chronic autoimmune skin disease that causes hair loss</td>
<td>Granted Breakthrough Therapy designation by the FDA</td>
<td>pfizer.com</td>
</tr>
<tr>
<td>ITF Pharma</td>
<td>TIGLUTIK™ (riluzole) oral suspension</td>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>Granted approval by the FDA</td>
<td>itfpharma.com</td>
</tr>
<tr>
<td>Baxter International, Inc.</td>
<td>Actifuse Flow Bone Graft Substitute</td>
<td>Orthopedic surgical procedures</td>
<td>Granted clearance by the FDA</td>
<td>baxter.com</td>
</tr>
<tr>
<td>AstraZeneca/MedImmune</td>
<td>Anifrolumbab</td>
<td>Moderate to severe lupus erythematosus (SLE)</td>
<td>Flunked Phase III clinical trial</td>
<td>astrazeneca.com</td>
</tr>
<tr>
<td>Horizon Pharma plc</td>
<td>Teprotumumab</td>
<td>Moderate-to-severe active thyroid eye disease (TED)</td>
<td>Early completion of enrollment for confirmatory Phase III trial</td>
<td>horizonpharma.com</td>
</tr>
<tr>
<td>SillaJen/Lee's Pharmaceutical Holdings</td>
<td>Oncolytic immunotherapy Pexa-Vec (formerly JX-594)</td>
<td>Advanced liver cancer</td>
<td>First patient enrolled in China in the Phase III PHOCUS clinical trial</td>
<td>pexavectrials.com</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
<td>Flortaucipir F 18, a Positron Emission Tomography (PET) imaging agent</td>
<td>Predicting brain tau pathology and Alzheimer's disease diagnosis</td>
<td>Phase III trial successfully met two primary endpoints</td>
<td>lilly.com</td>
</tr>
<tr>
<td>Advicenne</td>
<td>ADV7103</td>
<td>Distal Renal Tubular Acidosis (dRTA)</td>
<td>Granted Investigational New Drug (IND) clearance by FDA for ARENA-2 Phase III clinical trial</td>
<td>advicenne.com</td>
</tr>
<tr>
<td>Gilead Sciences and Galapagos NV</td>
<td>Filgotinib, a selective JAK1 inhibitor</td>
<td>Active ankylosing spondylitis (AS) in adults</td>
<td>Phase II TORTUGA clinical trial met endpoint of greater improvements in AS Disease Activity Score (ASDAS)</td>
<td>gilead.com</td>
</tr>
<tr>
<td>Neumentum</td>
<td>Non-opioid NTM-001 (pre-mixed bag ketorolac for continuous infusion)</td>
<td>Moderately severe acute pain</td>
<td>Completed dosing the first cohort of patients in its Phase I trial</td>
<td>neumentum.com</td>
</tr>
<tr>
<td>PvP Biologics, Inc.</td>
<td>Kuma062</td>
<td>Celiac disease</td>
<td>Two first-in-human clinical trials initiated</td>
<td>pvpbio.com</td>
</tr>
</tbody>
</table>
Research Center Spotlight is a monthly selection of clinical research centers who have Research Center Profile pages posted on CenterWatch.com. Included in their annual subscriptions, company profiles are randomly selected to appear in this section, providing added exposure for their expertise and services in conducting and managing clinical studies.

To learn more about becoming a Research Center Profile page subscriber, contact Sales at (617) 948-5100 or sales@centerwatch.com.

**Atrius Health, Inc.**
Boston, MA  
(617) 421-2175  
clinicaltrials@atriushealth.org

Atrius Health medical groups and home health agency & hospice work together (with hospital partners, community specialists and skilled nursing facilities) to develop innovative, effective, efficient ways to deliver care.

**Center for Clinical Studies, LTD. LLP.**
Houston, TX  
(713) 528-8818  
info@ccstexas.com

Founded by Drs. Stephen K. Tyring and Patricia Lee, CCS is a full-time private outpatient research facility that conducts Phase I-IV clinical trials for the pharmaceutical industry and government, as well as investigator initiated studies.

**Clinical Vision Research Center, SUNY College of Optometry**
New York, NY  
(212) 938-4052  
clinicrosearch@sunyopt.edu

CVRC partners with industry, foundations and government agencies to conduct patient-based eye and vision research. It provides a dynamic research environment, where advanced treatments can be rapidly tested and applied to enhance patient care.

**Global Medical Research**
DeSoto, TX  
(972) 996-5645  
recruitment@tarheelclinical.com

Global Medical Research focuses on Phase II-IV trials. Investigators have eight-plus years of clinical trial experience in areas including internal medicine, kidney disease, gastroenterology, endocrinology, hematology, pulmonary medicine, neurology and vaccine research.

**Great Lakes Medical Research**
Westfield, NY  
(716) 326-4890  
jferreira@glmr.info

Great Lakes Medical Research is a division of Westfield Family Physician, which provides a consistent and diverse patient population for clinical trials. The area’s limited clinical trial access provide ideal recruitment and retention.

**MDFirst Research**
Lancaster, SC  
(704) 491-1102  
akumar@mdfirstresearch.com

MDFirst Research is a clinical research center committed to helping sponsors meet and exceed patient recruitment, quality assurance and data integrity goals efficiently. It has extensive experience conducting Phase II-IV clinical trials of drugs and devices.

**Northwest Clinical Research Center**
Bellevue, WA  
(425) 453-0404  
regulatory@nwcrcc.net

NWCR is one of the largest independent research sites. Its research has been published in top medical journals and presented at national and international scientific meetings. Specialty: psychiatry and mood disorders.

**Oregon Urology Institute**
Springfield, OR  
(541) 284-5508  
stephanie@oregonurology.com

Oregon Urology Institute’s primary objective is to offer the finest urologic care for adult and pediatric patients, and give patients access to the latest pharmaceutical developments through clinical trial participation.

**University of Louisville Department of Cardiovascular Medicine Research Division**
Springfield, OR  
(541) 284-5508  
stephanie@oregonurology.com

The department is nationally recognized for its cardiac stem cell research and focus on treating heart failure. It’s a member of the Cardiovascular Cell Therapy Research Network, which has seven U.S. stem cell centers that conduct clinical trials on heart/vascular disease treatments.

**West Broward Research Institute, LLC.**
Lauderdale Lakes, FL  
(954) 530-5844  
kreese@wbri1.com

WBRI has formed a business research alliance with West Broward Nephrology and The Family Practice of West Broward. It’s main mission is to provide state of the art medical care and patient access to clinical trials.