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CNS Trial Failures Problematic but Fixable, Experts Agree

By Sony Salzman

The clinical research community is continuing to take a hard look at why trials of central nervous system treatments have such a high failure rate. The problems are easy to identify, experts say. What is needed are practical approaches to solving them.

The failure rate among CNS trials is second only to oncology. About 85 percent of CNS trials fail, compared to a failure rate of less than 70 percent in areas such as vaccine or ophthalmology trials.

The biggest cause of CNS trial failure is the "placebo response," says Mark Opler, chief research officer at WCG's MedAvante-ProPhase. When there's a strong placebo response — subjects who psychologically believe they are receiving benefits from the investigational drug even though they are unknowingly assigned to the trial's placebo arm — results can become muddled.

"A number of studies have suggested that placebo response rates are going up in neuroscience in general," Opler says, adding that the problem seems to be particularly pronounced in trials that look at pain and psychiatric medications.

A second, related problem is an over-reliance on subjective outcomes in lieu of more quantifiable biomarkers. Both of these problems make it less likely that a study will yield reliable, statistically significant results.

"The placebo response is more a problem in clinical [trials] with subjective endpoints rather than objective endpoints," explains Nathaniel Katz, Adjunct Associate Professor of Anesthesia, Tufts University School of Medicine, and founder of WCG's Analgesic Solutions.

When patients are asked to report pain on a scale of one to 10, for example, about one-third will not be able to rate their symptoms in a consistent way, Katz explains.

"So if you enroll them in a [trial], they're going to provide info that's not useful," he says. The good news is that there is a solution to this problem. Rather than toss out one-third of potentially eligible patients, you can put patients through a training course that helps them improve their ability to self-report pain. Katz has pioneered such training courses that already have been used to train more than 50,000 patients.

Furthermore, training patients to more accurately and consistently report on their own pain has a doubly beneficial effect, says Katz: "It inoculates them against the placebo response."

Another problem in CNS studies has to do with adherence to medication. In pain studies, says Katz, adherence rates can be as low as 50 percent. Medication adherence also is problematic in depression and other conditions that affect mood and behaviors.

Within CNS studies, he says, there are numerous examples of "clinical trials that

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Community, University, Industry Partner to Boost Minority Recruitment

A community-based initiative in West Philadelphia is blazing a trail for minority involvement in cancer trials, and academia and industry are signing on for the ride.

Currently more than 85 percent of people who enroll in clinical trials, on average, are white. Drug sponsors and researchers are increasingly worried that as precision medicine moves forward, the lack of minority awareness and participation in clinical trials will become an issue for drug development.

The nonprofit Lazarex Cancer Foundation and its Philadelphia neighborhood program, Community IMPACT, is providing services that help educate the local low-income population about clinical trials. At the same time, partners Drexel University and trials payment company Greenphire are learning about minority needs and attitudes toward clinical trials.

"I have nothing against middle-age white men, being one myself," says Jim Murphy, CEO of Greenphire. But "you want to test your medicines on a population that is reflective of the general populace."

It's not precisely the goal of Lazarex founder and CEO Dana Dornsife to get

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Regulatory Update

FDA Allows Analysis of Covariance for Randomized Control Trials

Drug sponsors can use complicated covariance analyses to help determine statistical significance or sharpen estimates of treatment efficacy, but they shouldn't apply those analyses to anything in a clinical trial that might be affected by the treatment, the FDA says in a new draft guidance.

The six-page draft guidance is the FDA's effort to round out recommendations in ICH's E9 Statistical Principle for Clinical Trials guidance. In it, regulators recognize that different patients have different disease prognoses and that drug sponsors would like to be able to incorporate different prognoses into statistical analyses of trial data.

When sponsors are writing out their protocols or statistical analysis plans, they should "prospectively specify the covariates and the mathematical form of the model."

Read the draft guidance here: https://bit.ly/2vlb6pl.

FDA Offers Clinical Guidance for Developing ADHD Meds

The FDA has released a draft guidance to guide sponsors developing stimulant drugs for attention deficit hyperactivity disorder (ADHD), outlining general considerations for trial design, clinical pharmacology and research involving pregnant women.

The guidance suggests several considerations for trial design. For example, it's a good idea for sponsors to include data from adequate studies in pediatric patients in their NDAs, as the disorder begins in childhood.

A single trial in adult patients can support adult indications, the agency says, because there is a sufficient similarity between the pathophysiology, disease characteristics and treatment outcomes for children and adults.

NDAs also should include data adequate to assess the drug's safety and effectiveness for patients four years of age and up. Sponsors should conduct one study in adolescent patients 13 to 17 years of age and one study in patients aged four to 12 to generate evidence of effectiveness.

Safety and effectiveness should be assessed using randomized, double-blind, placebo-controlled, parallel-group design trials, and sponsors should conduct at least one randomized, fixed-dose trial that examines more than one dose.

Flag Real-World Evidence in IND Applications, Guidance Says

Sponsors that plan to use real-world evidence in drug development must identify the sources of that evidence when requesting an IND from the FDA.

IND cover letters should indicate whether a sponsor hopes to use real-world evidence to support the safety or efficacy of a drug, to change a drug's label, or to comply with a postmarketing requirement, the agency says in a draft guidance released last month.

The guidance draws a line between real-world data — information about patients' health status or healthcare delivery "routinely collected from a variety of sources," including electronic health records, medical claims or billing data — and clinical evidence for a drug from analysis of real-world data.

Regulators only want to track real-world evidence that relate to specific products or regulatory decisions, so sponsors don't have to flag natural histories used to establish a clinical outcome test or biomarker, feasibility studies involving real-world evidence or studies that use real-world data "to perform exploratory analyses and generate hypotheses," the draft guidance states.

Read the draft guidance here: https://bit.ly/2LM1uPN.

FDA Releases Draft Guidance on Clinical Lactation

The FDA has published recommendations for drug sponsors planning trials that potentially will enroll breastfeeding women. The aim of the draft guidance issued last month is to protect the health and safety of research subjects and their babies.

The guidance specifies the circumstances that should lead sponsors to study the effects of a new investigational drug on lactation before enrolling women of reproductive age

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in a clinical trial. It also addresses approved drugs seeking a new indication that may be used by breastfeeding women.

Read the draft guidance here: https://bit.ly/2vR4AqB.

FDA Discusses Pilot Program for Single-Patient INDs

The FDA has launched a pilot program to help patients access needed investigational drugs outside of clinical investigations.

Project Facilitate, part of the agency's Expanded Access program, features a call center to help oncology providers navigate the process of obtaining permission for their seriously ill patients with no other treatment options left, including clinical trials.

"Access to clinical trials and access to novel therapeutics for patients is still a problem," said Richard Pazdur, director of the FDA's Oncology Center of Excellence, at a public workshop on the pilot program last month. "We know that not all oncologists or healthcare providers have the regulatory expertise or resources to navigate these single-patient IND processes."

The pilot program will give providers a single point of contact to guide them through the expanded access request process, helping them locate IRB resources, find the correct contact at the company that holds the IND for the requested treatment and complete the necessary FDA forms.

A public database tied in with the program also will list relevant information supplied by drug companies, including each company's policies on expanded access.

A secondary aim of Project Facilitate, Pazdur says, is to identify pharmaceutical companies who decline or have policies denying certain INDs and determine their reasoning.

Under the FDA's Expanded Access program, providers whose requests are approved have the status of physician-investigator — in a one-subject trial — and are required to follow all the agency's rules for conducting clinical trials.

In fiscal year 2017, the FDA approved all but five of the 1,637 expanded access requests it received.

Read materials from the May 16 public workshop here: https://bit.ly/2Q8OCBt.

Merck Flags Concerns on Widening Cancer Trial Eligibility

Merck is urging the FDA to look into potential safety concerns as the agency seeks to widen patient eligibility criteria for oncology drug trials of HIV, hepatitis B and hepatitis C patients.

In a comment on the agency's draft guidance on expanding trial eligibility criteria, the drugmaker cites concerns over immuno-oncology (IO) drugs because of the potential for serious immune reactions and impacts on liver function in patients with active viral infection.

The company suggests adding to the guidance "the availability of adequate safety data" as a consideration when developing eligibility criteria.

In another comment, the American Cancer Society Cancer Research Network recommends the FDA modernize eligibility criteria to ensure any racial or demographic group is not excluded, for instance, "upper age limits, or excluding comorbidities more highly associated with demographic or socioeconomic subgroup unless specific rationale for exclusion exists."

In total, the agency received nine responses in the public comment period, which ended May 13.

Read the draft guidance, Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, and comments here: https://bit.ly/2Jlpvet.

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CNS Trial Failures

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have failed. But if you look at the subgroup of patients who took their drug, the trial was successful." Once again, there are several techniques that have been demonstrated to bolster adherence, such as medication reminders and "smart" packaging.

Medication adherence problems in CNS studies is a "scandalous cause of failure," Katz says, "because it's so fixable."

CNS studies also may be more likely to fall victim to "trial shopping," a phenomenon in which patients enroll in multiple CNS studies simultaneously, or the same CNS study twice under two different names, often because of the financial incentives offered for trial participation.

Even as the industry struggles to grapple with the problem of duplicate patients, sites also may be recruiting truthful patients who still don't fit the study protocol, says Opler.

"In the rush to get warm bodies in clinical trials, we're putting the wrong people in," Opler says.

Another major challenge with CNS trials is the operational burden they place on study sites. The technology implemented to overcome problems like placebo effect places a greater burden on providers, meaning few research centers are incentivized to conducted CNS clinical research.

For six years, Sean Walsh, president of independent sites at WGC Clinical, ran an independent research site within a neurology practice. "Over those six years," Walsh says, "things to do in the studies just became more extensive and difficult."

For Alzheimer's disease studies alone, there might be more than a dozen different technology platforms investigators and staff would be asked to use for one study, he says.

"It just kept getting worse and worse," says Walsh. "The criteria had become so stringent that a lot of the PIs didn't want to do it anymore because none of the Phase III criteria married up to the standard of care. It's become so narrow and they want to hit so many secondary endpoints, that it's become impossible to find those patients."

This burden, "makes it less likely new investigators will get into these trials," agrees Opler. Investigator fatigue places a heightened imperative on pharma sponsors to carefully evaluate the utility of tech solutions and the complexity of CNS protocols.

Overall, many of the problems that contribute to CNS trial failure are fixable, experts agree. And considering the dearth of good therapies for CNS diseases, Opler notes that "a failed trial isn't just a scientific failure — it's also an ethical failure."

Minority Recruitment

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more minorities into clinical trials. The idea is to get care to people where they need it, as they need it, and in so doing, get them to become self-advocates.

"If we do the work here where they live," Dornsife says, "then we have a whole different conversation. Ultimately, we can change the face of cancer trials — literally."

A free clinic offering check-ups and routine blood pressure screening gives Lazarex and Drexel officials an idea of what West Philadelphia's predominantly minority residents need for healthcare. At the same time, residents are meeting doctors and trial recruiters and hearing about all their healthcare options if the news turns bad.

"If patients don't ask about clinical trials, the doctor is literally spending 11 minutes on them and they'll miss out," Dornsife says. "We need to provide resources for the community to empower them. We're removing barriers for people to ask."

Academic research benefits as well. "We are priming the pump for clinical trials groups," says Lucy Kerman, senior provost at Drexel University, which is housing the project on campus.

"Universities have huge expertise, but we don't always know the right questions to ask," Kerman says. Residents are "helping us learn how to listen. It's a radical disruption of what academic research looks like."

As founder and president of the Lazarex Cancer Foundation, Dornsife has spent years lobbying first governments and then drug companies to help make trials easier by paying patients' expenses — everything from airline tickets to parking stubs.

It took years and lots of hard work, but the efforts are paying off — last year, the FDA issued guidance saying that it didn't consider reimbursements to be inducements. Dornsife has since taken her case to the states. California and Pennsylvania have passed laws encouraging sponsors to help patients absorb the costs of trials, and bills are pending in Texas and Florida, with encouraging noises coming out of New York, Illinois and Ohio.

Greenphire recently announced it will link Lazarex with its ClinCard reimbursement technology, which offers a reloadable debit card that clinical trial participants can use to pay for trial-related expenses. Dornsife applauds Greenphire's contribution for lifting the burden of paper checks and manual reimbursement.

Wherever it's been tried, Dornsife's approach has turned the world upside down. In San Francisco and Los Angeles, a $500,000 sponsor investment led to a 74 percent improvement in minority enrollment. Seventy-eight percent of those patients had incomes under $25,000 per year.

Drug companies are noticing. Two years ago, Dornsife approached Amgen with the results of a pilot study in Boston that paid the minor expenses of trial recruits. The pilot improved overall enrollment by 29 percent — and doubled minority enrollment.

"Those were very compelling data points," says Eduardo Cetlin, executive director of philanthropy and responsibility at Amgen.

The Lazarex "recipe" was stunningly simple: First, reimburse for ancillary costs. Second, forge long-term partnerships with cancer centers. Third, engage in "culturally sensitive community outreach," Cetlin says. "We have a pretty dark history in this country with Tuskegee," Cetlin says. "You have to engage with people in a manner that they understand what's being offered and what the risks are."

Amgen was sold. The company has donated $2.5 million to Lazarex and Community IMPACT — and, most important to the program, the money doesn't come with any strings attached.

FDA Actions

The following is a sampling of FDA regulatory actions taken during the previous month, compiled from CenterWatch and third-party sources including the FDA and company press releases. For more information on FDA approvals, visit centerwatch.com/drug-information/fda-approvals. For custom drug intelligence reports, email marketresearch@centerwatch.com. Join the LinkedIn Drug Research Updates group linkedin.com/groups/3224258/.

Company name	Drug name	Indication	FDA action
Belite Bio	LBS-008 (BPN-14967)	atrophic age-related macular degeneration and Stargardt disease	IND approval granted
AVROBIO, Inc.	AVR-RD-01	Fabry disease	IND approval granted
BioLineRx Ltd.	AGI-134	solid tumors	IND approval granted
Transgene	TG4050	ovarian cancer	IND approval granted
Knopp Biosciences, LLC	dexpramipexole	hypereosinophilic syndrome (HES)	Orphan Drug Designation granted
Bayer	darolutamide	non-metastatic castration-resistant prostate cancer (nmCRPC)	Priority Review designation granted
GlaxoSmithKline	Benlysta (belimumab) intravenous (IV) infusion	pediatric systemic lupus erythematosus (SLE)	Priority Review designation granted
Purdue Pharma, L.P.	nalmefene hydrochloride (HCl) injection	emergency treatment of known or suspected opioid overdose	Competitive Generic Therapy (CGT) designation granted
NeuroSigma, Inc.	Monarch eTNS System (Monarch)	attention deficit hyperactivity disorder (ADHD)	Clearance granted
AliveCor	KardiaMobile 6L six-lead personal ECG device	cardiovascular disease	Clearance granted
Merz Americas	XEOMIN (incobotulinumtoxinA)	blepharospasm (involuntary blinking)	sBLA approval granted
United Therapeutics Corporation and XVIVO Perfusion, Inc.	XPS and STEEN Solution	ex-vivo lung perfusion (EVLP)	PMA approval granted
Viela Bio	inebilizumab	neuromyelitis optica spectrum disorder (NMOSD)	Breakthrough Therapy Designation granted
GENFIT	elafibranor	Primary Biliary Cholangitis (PBC) in adult subjects with inadequate response to ursodeoxycholic acid (UDCA)	Breakthrough Therapy Designation granted
Concept Medical, Inc.	MagicTouch Sirolimus drug-coated balloon (DCB) catheter	coronary in-stent restenosis (ISR)	Breakthrough Device Designation granted
Moleculin Biotech, Inc.	Annamycin	relapsed or refractory acute myeloid leukemia (AML)	Fast Track Designation granted
Phoenix Tissue Repair, Inc.	PTR-01	recessive dystrophic epidermolysis bullosa (RDEB)	Fast Track Designation granted
Finch Therapeutics Group, Inc.	Full-Spectrum Microbiota (FSM)	pediatric Autism Spectrum Disorder (ASD)	Fast Track Designation granted
Savara, Inc.	Molgradex	autoimmune pulmonary alveolar proteinosis (aPAP)	Fast Track Designation granted

Company name	Drug name	Indication	FDA action
Merck	KEYTRUDA in combination with Inlyta (axitinib)	chronic obstructive pulmonary disease (COPD)	Approved
Teva Pharmaceutical Industries Ltd.	generic naloxone hydrochloride nasal spray	peripheral arterial disease (PAD)	Approved
AbbVie	SKYRIZI (risankizumab-rzaa)	moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	Approved
Boston Scientific Corporation	LOTUS Edge Aortic Valve System	severe aortic stenosis	Approved
BAROnova, Inc.	TransPyloric Shuttle (TPS) Device	obesity	Approved
Samsung Bioepis Co., Ltd.	ETICOVO (etanercept-ykro)	rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis and polyarticular juvenile idiopathic arthritis	Approved
Regeneron Pharmaceuticals, Inc. and Sanofi	Praluent (alirocumab)	reduce the risk of heart attack, stroke and unstable angina requiring hospitalization in adults with established cardiovascular (CV) disease	Approved
Bausch Health Companies, Inc.	DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%	plaque psoriasis in adults	Approved
Vertex Pharmaceuticals, Inc.	KALYDECO (ivacaftor)	cystic fibrosis (CF) in children ages six months to less than 12 months	Approved
AbbVie, Inc.	Mavyret (glecaprevir and pibrentasvir) tablets	six genotypes of hepatitis C virus (HCV) in children ages 12 to 17	Approved
Medtronic plc	Attain Stability Quad MRI SureScan left heart lead	CRT treatment for heart failure	Approved
Genentech	Kadcyla (ado-trastuzumab emtansine)	adjuvant treatment of people with HER2-positive early breast cancer (EBC) who have residual invasive disease after neoadjuvant taxane and Herceptin (trastuzumab)-based treatment	Approved
Dr. Reddy's Laboratories Ltd.	Testosterone Gel 1.62% (20.25 mg/1.25 g pump actuation)	testosterone deficiency	Approved
Boston Scientific	VICI VENOUS STENT System	iliofemoral venous obstructive disease	Approved
Genentech and AbbVie	Venclexta (venetoclax) in combination with Gazyva (obinutuzumab)	previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	Approved
EMD Serono and Pfizer, Inc.	BAVENCIO (avelumab) in combination with INLYTA (axitinib)	advanced renal cell carcinoma (RCC)	Approved
Eli Lilly and Company	CYRAMZA (ramucirumab injection, 10 mg/mL solution)	hepatocellular carcinoma (HCC)	Approved
Regeneron Pharmaceuticals, Inc.	EYLEA (aflibercept) Injection	diabetic retinopathy (DR)	Approved

Study Lead Opportunities

CenterWatch analyzes data in its drug intelligence database to provide advance notice of clinical trials expected to enter the next phase of clinical development soon. Contact information is provided for follow up. **Sponsors/CROs:** to list an upcoming trial here, contact Leslie Ramsey, (703) 538-7661, lramsey@fdanews.com; or to initiate a search to identify sites for an upcoming or currently active trial, email trialwatch@centerwatch.com or submit online at centerwatch.com/clinical-trials/trialwatch/. **Sites:** to be matched to sponsor/CRO requests, submit a brief online profile at centerwatch.com/news-resources/trialwatch/.

Drug name	Indication	Company name	Contact information
Phase I			
AVID200	myelofibrosis (MF)	Forbius	Ilia A. Tikhomirov info@forbius.com
XmAb23104	advanced solid tumors	Xencor, Inc.	Charles Liles cliles@xencor.com
SL-279252 (PD1/OX40L)	advanced solid tumors and lymphomas	Shattuck Labs, Inc.	Andrew R. Neill VP, Corporate Development and Strategy shattuckmedia@shattucklabs.com
AL002	Alzheimer's disease	Alector, Inc.	alector.com
TP-3654	advanced solid tumors	Tolero Pharmaceuticals, Inc.	toleropharma.com
TPST-1120	advanced solid tumor malignancies	Tempest Therapeutics Inc.	Steve Edelson sedelson@versantventures.com
ORIC-101 in combination with nab-paclitaxel	advanced solid tumors	ORIC Pharmaceuticals	Krys Corbett info@oricpharma.com
Phase II			
BPN14770	early Alzheimer's disease (AD)	Tetra Discovery Partners	Mark Gurney, Ph.D. Chief Executive Officer info@tetradiscovery.com
AXO-Lenti-PD	Parkinson's disease	Axovant Gene Therapies, Ltd.	Mike Beyer Sam Brown Inc. mikebeyer@sambrown.com media@axovant.com
TVB-2640	non-alcoholic steatohepatitis (NASH)	3-V Biosciences, Inc.	3vbio.com
OMT-28	persistent atrial fibrillation (AF)	OMEICOS Therapeutics	Dr. Robert Fischer CEO, CSO r.fischer@omeicos.com
IFX-1	ANCA-associated vasculitis (AAV)	InflaRx	Katja Arnold inflarx@mc-services.eu
Phase III			
cabozantinib (CABOMETYX) in combination with nivolumab (Opdivo) and ipilimumab (Yervoy) versus nivolumab and ipilimumab	previously untreated advanced renal cell carcinoma (RCC)	Exelixis	Lindsay Treadway Senior Director, Public Affairs and Advocacy Relations ltreadway@exelixis.com
TJ202/MOR202	relapsed or refractory multiple myeloma	I-Mab Biopharma and MorphoSys AG	Raven Lin Vice President of Corporate Development raven.lin@i-mabbiopharma.com Dr. Sarah Fakih Head of Corporate Communications & IR investors@morphosys.com
pimavanserin	major depressive disorder (MDD)	ACADIA Pharmaceuticals, Inc.	Maurissa Messier media@acadia-pharm.com
fostamatinib disodium hexahydrate (fostamatinib)	warm antibody autoimmune hemolytic anemia (AIHA)	Rigel Pharmaceuticals, Inc.	David Burke dburke@rigel.com
RGN-259 eye drops	dry eye syndrome	ReGenTree, LLC	regentreellc.com

