Human Experience, Analytical Systems Join to Strengthen Trials

By Leslie Ramsey

Drawing objective conclusions from subjective measurements is a common challenge in pain management research and one that can lead to skewed results without a system to analyze data, spot problems and evaluate their impact.

But identifying aberrations is not the only challenge, says Arturo Morales, chief technology and data officer for WCG Analogic Solutions. “It’s very easy to tell that one thing is not like the others. But merely looking at data and saying, ‘This one looks different,’ describes the way people have been approaching monitoring in clinical trials for years.”

That approach is no longer enough. Today’s trials require more sophisticated approaches that overcome the data quantity and quality challenges and requirements inherent in machine learning tools, Morales says. Statistical process control (SPC), a technique borrowed from the manufacturing and quality domains is one of those approaches. SPC, combined with a clinical review done by central clinical and statistical monitors, can be used to cull through clinical data and look for differences that are mathematically significant and clinically relevant. This approach, he says, then allows for the incorporation of human experience and judgment to interpret those differences, their impact on outcomes and the implementation of interventions to mitigate risks to study outcomes.

Consider the sheer quantity of variables in today’s trials, Morales says. Only a handful are seen in traditional monitoring. Software and technology are now looking at thousands of variables, he says, and this is creating a new approach to data monitoring.

GCP Questions, FDA Answers: Transfer of Study Records

The FDA’s Office of Good Clinical Practice responds to inquiries on a variety of trial-related subjects, providing answers on the agency’s official regulations as well as best practices. The following is one such question and answer excerpted from the CenterWatch publication, GCP Questions, FDA Answers.

Question: I have a question on a situation where a study has finished and all patient study activities are complete (only data cleaning and close out activities to occur), but the PI (MD) is retiring and closing his research facility. The PI is a part of a large multi-site practice and has a partner (MD) within the overarching practice who is conducting the same study as a PI a few miles down the road at one of the other clinics. All patients recruited came from their practice where both MDs have access to the medical records. The retiring PI sent a letter to the subjects stating he is closing his practice and the remaining study activities would be finished by the partner who is also conducting the study. Would the retiring PI have to get subject consent to transfer each subject’s study record to the new PI? Or would that typically be covered in the study consent document? I have confirmed that the data privacy statement signed by each of the patients as a part of them being a patient of the practice covers the transfer of the medical records.

See GCP Questions, FDA Answers on page 6 >>
Up and Coming

This feature highlights changes in clinical research organizations’ personnel.

Accelerate Diagnostics
Accelerate Diagnostics has named Jack Phillips chief operating officer. Phillips previously served as president and chief executive officer at Roche Diagnostics.

Allogene Therapeutics
Rafael Amado has been appointed executive vice president of research and development and chief medical officer at Allogene Therapeutics. Amado was most recently president of research and development at Adaptimmune.

Altasciences
Beatrice Setnik has been named chief scientific officer at Altasciences. Setnik was previously vice president, scientific and medical affairs, at Syneos Health.

Aprea Therapeutics
Aprea Therapeutics has named Scott Coiante senior vice president and chief financial officer. Coiante was previously senior vice president and CFO at Agile Therapeutics.

Assembly Biosciences
Assembly Biosciences has named John McHutchison president and chief executive officer. McHutchison most recently served as chief scientific officer and head of research and development at Gilead Sciences.

Astellas
David Fryrear has been named senior vice president and head of the clinical research and quality assurance organization at Astellas. Fryrear was previously senior director, R&D quality assurance — clinical, PV, RA and knowledge management at AbbVie.

CeloNova Biosciences
Carl St. Bernard has been appointed president and chief executive officer of CeloNova Biosciences. St. Bernard was previously president and CEO of Tryton Medical.

Cleave Therapeutics
Amy Burroughs has been appointed chief executive officer and Scott Harris has been named chief operating officer at Cleave Therapeutics. Burroughs was most recently executive-in-residence at SAM Ventures and a strategic commercial advisor to Crintecis Pharmaceuticals. Harris was most recently executive vice president, corporate development and operations, at Navire Pharma.

Codexis
Codexis has appointed Ross Taylor as senior vice president and chief financial officer, effective August 19. Taylor was previously CFO at Abaxis, Inc.

Crucial Data Solutions
Jeff Rogers has been named president at Crucial Data Solutions. Rogers was most recently chief commercial officer at Trialbee.

Emalex Biosciences
Emalex Biosciences has named Atul Mahableshwarkar senior vice president of drug development. Mahableshwarkar is a board-certified adult psychiatrist and was formerly an associate professor and vice chair of the Department of Psychiatry and Behavioral Sciences at the Chicago Medical School of Rosalind Franklin University.

Foundation Medicine
Priti Hegde has been named chief scientific officer at Foundation Medicine. Hegde was most recently senior director and principal scientist in oncology biomarker development at Genentech.

Glauc0nix Biosciences
Kimberly Southern has been appointed chief operating officer at Glauc0nix Biosciences. Southern was previously COO at New England Peptide.

InMed Pharmaceuticals
Bruce Colwill has been appointed chief financial officer at InMed Pharmaceuticals. Colwill was previously chief financial officer at General Fusion.

Nimbus
Bret Boudousquie has been appointed chief executive officer at Nimbus. Boudousquie was previously president of RadiaDyne.

Palladio Biosciences
Palladio Biosciences has named Alex Martin chief executive officer. Martin most recently served as CEO of Realm Therapeutics.

Parexel
Parexel has announced the appointment of Gavin Nichols as executive vice president, informatics and information technology. Nichols was formerly chief information officer and executive vice president of technology at BioClinica.

PROMETRIKA
PROMETRIKA has named Barry Mirrer as head of quality assurance. Mirrer was
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Up and Coming (continued from page 2)

previously global head, quality management,
for IQVIA.

Reliv International
Alfredo Galvez has been appointed chief
scientific advisor at Reliv International.
Galvez was formerly CSO at SL Tech, a Reliv
subsidary.

Ribon Therapeutics
Sudha Parasuraman has been named chief
financial officer and Edward “Tad” Stewart has
been appointed chief business officer at Ribon
Therapeutics. Parasuraman was most recently
CMO for X4 Pharmaceuticals. Stewart previously
served as CBO for Crescendo Biologics.

Rodin Therapeutics
Rodin Therapeutics has named Ajim
Tamboli as chief financial officer. Tamboli
most recently focused on life sciences in-
vesting at Asymmetry Capital Management.

Serimmune
Noah Nasser has been named chief execu-
tive officer at Serimmune. Nasser previously
was chief commercial officer at San Diego
biotechnology company, Human Longevity.

Silence Therapeutics
Silence Therapeutics has announced that
Jorgen Wittendorff has been named head
of manufacturing. Wittendorff most recently
served as senior director, CMC manufactur-
and product supply at Ablynx.

SQZ Biotech
SQZ Biotech has appointed Teri Loxam
chief financial officer. Loxam was previously
senior vice president of investor relations
and global communications at Merck & Co.

Veravas
Veravas has announced the appointment of
Carroll Streetman as chief executive officer.
Streetman was previously global vice president
and chief marketing officer, oncology, at Eli Lilly.

Vor Biopharma
Robert Ang has been appointed president
and chief executive officer at Vor Biopharma.
Ang is the former chief business officer of
Neon Therapeutics.

Worldwide Clinical Trials
Worldwide Clinical Trials has named Hiromi
Wakita vice president of clinical operations.
Wakita will lead the company’s operations
in Japan. He previously held the position of
Japan general manager for Clinipace.
WCG Clinical Announces Acquisition of PharmaSeek

WCG Clinical has acquired clinical trial services organization PharmaSeek LLC, including its PFS Clinical and PatientWise subsidiaries, WCG announced last week.

Madison, Wisconsin-based PharmaSeek provides trial administration support and consulting as well as patient recruitment and training services. The company serves trial sites, multi-specialty practices, integrated health systems and academic medical centers.

Probability Platform Helps Predict Trials’ Regulatory Success

Evaluate Ltd. has developed an algorithm to predict the regulatory success of investigational drug products by combining industry and market data with individual products’ specific characteristics.

Called Product Specific PTRS, the tool aims to help sponsors evaluate the viability of their drug candidates and determine those that are not likely to make it through regulatory approval.

The tool is integrated with the company’s EvaluatePharma Vision service, which provides forecasting data, clinical timelines and sales predictions.

Javara Teams with Local Practice to Bring Trials to Patients

North Carolina-based clinical research organization Javara is teaming with a local medical practice to involve it in clinical trials that meet its patients’ needs.

Javara will place trial coordinators in Charlotte, N.C.-area Tryon Medical Partners clinics to help identify specific trials Tryon patients can participate in. Beginning in two of Tryon’s eight locations next month, Javara initially will focus on trials in endocrinology, internal medicine and dermatology and hopes to grow to 35 to 45 trials in the next 18 months.

Tryon’s 89 internists and specialists serve approximately 110,000 patients.

FDA Releases Guidance on Drug Development for Fabry Disease

The FDA has okayed the use of a single trial to prove efficacy of any drug developed to treat Fabry Disease, according to a draft guidance the agency issued last week.

Sponsors should think about combining multiple clinical outcomes in their assessments given FD’s multi-systemic nature, highly variable rate of progression and heterogeneity, advises the guidance which focuses on trial design, efficacy endpoints and eligibility criteria.

If the drug is meant to slow or arrest disease progression but not reverse it, the trial should last long enough to observe disease progression in the control group, the guidance says.

Eligible patients should have the diagnosis confirmed through both biochemical testing and molecular genetic testing, and sponsors should think about enrolling pedi atric patients in trials as early as possible.

Comments on the draft guidance are due by October 7.

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

Sarepta’s “Erroneous” AER Proves Costly

Sarepta Therapeutics’ stock plummeted 12.6 percent Thursday following an adverse event report (AER) of a serious side effect during a phase 2 gene therapy trial – but the company says the AER was wrongly submitted.

The sponsor says that neither it nor the trial’s principal investigator reported an adverse event involving a participant who experienced rhabdomyolysis. The participant in Sarepta’s trial, which is testing a micro-dystrophin gene therapy candidate for Duchenne muscular dystrophy, was hospitalized for observation and determined to be asymptomatic.

“While Sarepta and its principal investigator remain blinded to the study,” the company says, “the study drug safety monitoring board is unblinded to the event and has reviewed the issue and recommends the study continue uninterrupted.”

The submitter of the AER has not been identified.

Veristat Opens Office in Taiwan

Veristat has opened a new facility in Taipei, Taiwan, for its clinical trial, biostatistics and programming operations.

The new location will house a team of statistical programmers and clinical trial professionals to meet the increasing demand for local and international regulatory submission support in the region.
Human Experience

likely to have a direct impact on the outcome.
If you try to tackle the task without the systems
to help you, you are quickly overwhelmed by
the number of signals, the amount of work,
the quantity of data and the challenge of
consistently applying interventions to avoid
introducing bias in the study.

But you also need to formulate solutions. “No
machine, no matter how learned or intelligent,
can handle that task,” he says. “You need human
knowledge to make sense of the data.”

Focusing on too large a set of variables will
lead to many signals that are clinically irrelevant,
Morales says. “We aren’t looking for every
questionable blip on the radar. The key is that
we know which blips are likely significant.” For
example:

- **In a patient:** Extreme variability in daily
  symptom reporting or discordance between
caregiver and clinician assessments of the same
symptom;
- **At a particular site:** An outlier site with mul-
tiple subjects with high anxiety scores;
- **Across the entire study:** A change over
time in perceived disability scores or number of
adverse events.

Humans select those metrics, focusing on
things that have a reason to be looked at, not
just a bunch of variables that may or may not be
relevant. After all, variation itself isn’t a bad thing.
Aberrations that may be mathematically relevant
aren’t necessarily clinically relevant, Morales says.

Analgesic Solutions’ answer to the challenge
is its Quantitative Data Surveillance System
(QDSS), which combines SPC with interpretation
and analysis by a team of clinical experts – trial
monitors, clinicians, subject matter experts, etc. –
appropriate to the individual trial. Then, working
with trial staff and a sponsor, the team comes
up with recommendations on what to do based
on clinical operations, disease knowledge and
regulatory expertise.

But timing is key. Waiting until the trial is
completed and the database locked leaves you
with no recourse if you find a problem. “In the
past,” Morales says, “you set up your trial, and
you hoped you designed your protocols per-
fectly and the sites executed them accurately.
Then you closed your eyes and hoped for the
best for two years.”

“Today, sponsors and CROs can look under
the hood while the trial is running and blinded
and identify threats to the outcome of the study,”
he says. “That’s a monumental change.”

The QDSS goal is to systematically and con-
sistently recommend the mitigation strategies
and actions to correct data problems. The system
allows you to triage the problem in real-time and
act while you still have the opportunity to make
changes. “You have to stop the bleeding first”
Morales says.

For example, at some sites — due to an
apparent decrease in data quality in patient-re-
ported outcomes – staff and patients may need
more training in accurate symptom reporting.
This training will refresh them on key concepts
shown to have an impact on data quality and
thus can potentially improve the outcome of the
study.

Other solutions QDSS might propose include
adjusting screening criteria to recruit more accu-
rately or monitoring specific sites for procedural
problems.

Beyond helping current trials, QDSS can use
the lessons it learns to make future trials better,
Morales says. “The learnings we derive from past
trials can increase sensitivity earlier and optimize
the variables we look at and how we look at
them for clinical relevance.” Using that approach,
he says, bias is minimized by standardizing
analysis and responses.
GCP Questions, FDA Answers
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**Answer:** You should check with your reviewing IRB and your institutional officials regarding the transfer of records from one PI (clinical investigator) to another PI both from the same practice. The informed consent might need to be changed as the new PI would need to be listed as a contact in case the subject experiences an adverse event from the investigational product. I would also think that the subjects should be informed that the other PI will be taking over. This communication can be review and approved by the IRB.

Additionally, the sponsor should notify FDA that one of the PIs is retiring. They can consult FDA regulatory practice manager (RPM) for the IND. Below is some general information regarding transfer of study records.

GCP requires that documentation of study data be accurate, complete, legible and timely. Any changes or corrections should be dated, initialed and explained and should be made in a manner that does not obscure the original entry (that is, an audit trail should be maintained). The study records should be adequate to demonstrate how the study was actually conducted.

Data used in any analyses must be traceable back to the records maintained at the clinical sites.

Complete transparency is important. Please note that site 1 needs to maintain records of the patient up to the time of transfer and should note in the site’s records that the patient transferred to site 2 and when this occurred. Site 2 should receive copies of the patient’s records from site 1 and document in their records that the patient transferred from site 1 and when the transfer occurred. The sponsor records should also reflect this transfer.

Also, it is not clear to me even if the study is from one practice (two PIs) that a closeout needs to be completed for the PI who is retiring. Again, you should consult your RPM for the IND. FDA does not have a guidance document that provides details about how to close out a study. However, the following information is found in the guidance ICH E6(R2) Good Clinical Practice at https://bit.ly/31uhxES.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor’s office. A final closeout of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

For more information on GCP Questions, FDA Answers, click here: https://bit.ly/2OFHCyT.
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<td>Precigen, Inc.</td>
<td>PRGN-3005 UltraCAR-T</td>
<td>advanced, recurrent platinum resistant ovarian, fallopian tube or primary peritoneal cancer</td>
<td>Phase 1 trial initiated</td>
<td>precigen.com</td>
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<tr>
<td>Soricimed Biopharma, Inc.</td>
<td>SOR-C13</td>
<td>late stage pancreatic cancer</td>
<td>Phase 1b trial initiated enrolling 63 subjects</td>
<td>soricimed.com</td>
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<td>89Bio Ltd.</td>
<td>BIO89-100</td>
<td>nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) and high risk of NASH</td>
<td>Phase 1b/2a trial initiated enrolling 83 subjects</td>
<td>89bio.com</td>
</tr>
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<td>Provention Bio, Inc.</td>
<td>PRV-3279</td>
<td>lupus</td>
<td>Phase 1b/2a trial initiated enrolling 16 healthy volunteers</td>
<td>proventionbio.com</td>
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<td>Eureka Therapeutics, Inc.</td>
<td>ET140202 ARTEMIS T-Cell therapy</td>
<td>advanced hepatocellular carcinoma (HCC) liver cancer</td>
<td>Phase 1/2 trial initiated enrolling subjects with metastatic or locally advanced, inoperable liver cancer and have progressed or have not been able to tolerate at least one line of treatment at City of Hope in Duarte, CA</td>
<td>eurekatherapeutics.com</td>
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<td>RegeneRx Biopharmaceuticals, Inc.</td>
<td>RGN-137</td>
<td>epidermolysis bullosa (EB)</td>
<td>Phase 2 trial initiated</td>
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<td>POXEL SA</td>
<td>PXL770</td>
<td>NASH</td>
<td>Phase 2a trial initiated enrolling 100 subjects with nonalcoholic fatty liver disease (NAFLD) who likely have NASH at sites in the U.S.</td>
<td>poxelpharma.com</td>
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<tr>
<td>Altavant Sciences</td>
<td>rodaritstat ethyl</td>
<td>pulmonary arterial hypertension (PAH)</td>
<td>Phase 2a trial initiated enrolling 36 subjects</td>
<td>altavant.com</td>
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<tr>
<td>Astellas Pharma, Inc.</td>
<td>fezolinetant</td>
<td>moderate-to-severe vasomotor symptoms (VMS)</td>
<td>Phase 3 trial initiated enrolling 450 subjects at 20 sites in the U.S., Canada and Europe</td>
<td>astellas.com/us/</td>
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<tr>
<td>Apyx Medical Corporation</td>
<td>next-generation J-Plasma Precise Handpiece</td>
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<td>apyxmedical.com</td>
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<td>Alnylam Pharmaceuticals, Inc.</td>
<td>givosiran</td>
<td>acute hepatic porphyria (AHP)</td>
<td>Priority Review granted by the FDA</td>
<td>alnylam.com</td>
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<td>Provention Bio, Inc.</td>
<td>teplizumab (PRV-031)</td>
<td>prevention or delay of clinical type 1 diabetes (T1D) in at-risk individuals</td>
<td>Breakthrough Therapy designation granted by the FDA</td>
<td>proventionbio.com</td>
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<td>Inotrem S.A.</td>
<td>nangibotide (LR12)</td>
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<td>inotrem.com</td>
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<td>Daiichi Sankyo</td>
<td>Turallo (pekidartinib) capsules</td>
<td>subjects with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not responsive to improvement with surgery</td>
<td>Approval granted by the FDA</td>
<td>daiichisankyo.com</td>
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<tr>
<td>Bracco Diagnostics, Inc.</td>
<td>VARIBAR THIN LIQUID (barium sulfate) for oral suspension</td>
<td>dysphagia</td>
<td>Approval granted by the FDA</td>
<td>braccoimaging.com</td>
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Miami, FL  
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samaba@advancedpharmacr.com

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## ALAS Science Clinical Research
Henderson, NV  
(702) 570-0272  
info@viableresearch.org

Alas Science Clinical Research, conducts clinical trials in diabetes and other health-related conditions (Cardiovascular, metabolic disorders, neuropathies, obesity and medical devices). The organization has been conducting clinical trials since September 2004.

## Clinical Research of West Florida, Inc. – Tampa
Tampa, FL  
(813) 870-1292  
bkeskiner@crwf.com

Clinical Research of West Florida, Inc. provides improved and innovative healthcare opportunities to residents through clinical research studies. CRWF works with board certified/eligible community-based physicians to conduct phase 1-4 clinical research trials.

## ClinOhio Research Services, LLC
Columbus, OH  
(614) 668-6630  
jsanders@clinohioresearch.com

ClinOhio Research Services is an independent, multi-therapeutic, dedicated outpatient research site established in 2017. With a wide range of capabilities to support the conduct of clinical studies and provide high quality data, their investigators provide access to over 70,000 patients.

## DJL Clinical Research
Charlotte, NC  
(704) 247-9179  
jen.ponder@djlresearch.com

The goal of DJL Clinical Research is to assist in the clinical research of innovative medicines. They are committed to creating an environment that cares for, respects and values people from diverse backgrounds which enables all patients to receive outstanding medical care.

## Einstein-Montefiore Institute for Clinical and Translational Research
Bronx, NY  
(718) 430-2500  
ictreinstein.yu.edu

The Einstein-Montefiore Institute enhances the discipline of clinical and translational research by promoting multidisciplinary collaboration, addressing translational ‘blocks’in research and providing infrastructure.

## Health Concepts
Rapid City, SD  
(605) 348-4141  
healtheconcepts104@hotmail.com

Health Concepts is a state of the art research center built in 2009 with complete technology for a wide range of research studies. Health Concepts has infusion capabilities and recent construction lends itself for device research.

## JBR Clinical Research
Salt Lake City, UT  
(801) 261-2000  
jhunt@jbrutah.com

JBR Clinical Research had conducted clinical trials for over 15 years and has developed unique methods for drug efficacy assessment. A pioneer in clinical research, JBR continues to lead in phase one through four studies.

## Memorial Health University Medical Center
Savannah, GA  
(912) 350-8707

Memorial Health has more than 50 physicians in various specialties participating in research. All principal investigators are board certified in their specialties. Many have 10 to 15 years of experience in clinical trials.

## Northern Light Eastern Maine Medical Center
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The Center's professional staff provides support to investigators throughout the system who have innovative ideas for research in clinical, epidemiological, behavioral, health services and outcomes-oriented research.