Build Quality into Trials from the Beginning to Avoid Disaster

By Colin Stoecker

Quality principles should be incorporated into clinical trial design from the beginning, says one pharma executive, to save time and money and avoid disasters that could cripple a trial.

More than 16 percent of new drug submissions to the FDA are severely impacted by quality issues and 32 percent of first-cycle submissions fail due to quality-related issues, Sharon Reinhard, executive director of Merck Research Labs Quality Assurance, told attendees at the 14th Annual FDA Inspections Summit last week. Of that 32 percent, 53 percent never win approval and 47 percent experience a median delay of 14 months, she said.

Reinhard has seen her share of quality disasters, and told her audience how a quality by design approach could have averted those failures.

In what she calls “Randomization Schedule Disaster #1,” Reinhard tells the story of a data manager at a CRO who was hired to create a randomization schedule for a pivotal trial. Mistaking the completed randomization schedule for another document, the manager accidentally emailed the schedule to the entire study team, which was supposed to be double-blinded.

Reinhard used the example to point to a failure in the CRO’s standard operating procedures — key documents were not required to be password protected or stored in a firewall-protected area.

Using the QBD approach, the randomization schedule could have been identified as a median delay of 14 months, she said.

Giving Patients Back Their Voice in Clinical Trials

By Colin Stoecker

When clinical trial participants talk about how they feel entering a study, three words stand out: vulnerable, overwhelmed, disconnected.

If sponsors want to commit fully to engaging patients in their trials, they need to focus on providing an experience that is the opposite of those three words, making patients feel safe, supported and included.

Clinical trial experts and patient advocates discussed ways to achieve that approach to the patient at the 2019 WCG Patient Advocacy Forum in Washington, D.C., last week.

The number one thing sponsors overlook, says trial veteran and author Mary Elizabeth Williams, is that once a patient is diagnosed with a disease, the patient’s whole world changes.

“No matter how much agency you have and confidence, when you become a patient, you instantly become vulnerable,” said Williams, a survivor of metastatic melanoma.

“You sit there in a paper gown with no shoes,” she said, “and the doctor will tell you what to do, and what you can’t and when.” Patients become passive vessels for testing drugs and have no voice: their only role is to take orders.

Patients need to feel they have made an active decision to participate in research, not just that a trial is their last and only chance. “We consent to clinical trials like we do to the updated terms of service”
Biogen Resurrects Alzheimer’s Drug for FDA Approval

Biogen has decided to renew its bid for FDA approval in early 2020 of its investigational anti-amyloid Alzheimer’s drug aducanumab after halting clinical trials earlier this year.

Following discussions with the FDA about using data gathered after the trial ended, the company has reassessed its phase 3 trials of aducanumab, concluding that the longer-term exposure to the drug in one trial succeeded in reducing decline in Alzheimer’s patients.

Biogen’s EMERGE and ENGAGE trials were initiated in 2015 with the same dosage, but data from the ENGAGE trial assessed after only 18 months indicated negative effect compared to placebo and led Biogen to halt the study (CenterWatch Weekly, April 29, 2019).

The new, larger dataset provided longer-term results and showed a statistically significant reduction of clinical decline in EMERGE, Biogen says, and a small subset of ENGAGE results would have followed suit. For more information on Biogen’s decision, click here: https://bit.ly/2Jc0y36.

FDA Clarifies Its Approach to Postmarket Studies and Clinical Trials

In a draft revision of an April 2011 guidance, the FDA has laid out its current thinking on when the agency may require postmarket studies or clinical trials for approved prescription drugs.

The draft adds new information on when the FDA’s Adverse Event Reporting System (FAERS) and Vaccine Adverse Event Reporting System (VAERS) may be sufficient for identifying and assessing new serious adverse drug events that “occur rarely and are closely linked in time to the initiation of the drug and for which the background rate of events is low,” the draft says.

Certain questions related to serious risk “may only be answerable through specific types of studies or clinical trials,” the agency says. For example, animal studies or clinical pharmacokinetic and pharmacodynamic trials may be the only way to determine if a drug is carcinogenic or could potentially interact with other treatments.

The agency uses the term postmarket- ing requirement (PMR) to cover all required postmarket studies or clinical trials. PMR’s aim to “more fully characterize a serious risk, if one exists.”

The agency will review data and information from a PMR to “assess its effect on the benefit-risk profile of the drug,” which may result in labeling changes.

The Substance Use–Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) of 2018 required the agency to issue new guidance on when it may call for postmarket studies or trials.

Read the revised draft guidance here: https://bit.ly/345TYDD.

Innovation Needed to Cure Rare Diseases, Says Sharpless

Sponsors need to be innovative in their approach to developing therapies for rare diseases, Acting FDA Commissioner Ned Sharpless said last week at the 2019 National Organization for Rare Diseases (NORD) meeting.

The FDA recently has provided support for several initiatives on the study of rare diseases, including $4.1 million for two research grants to fund a natural history study of rare diseases such as medullar thyroid cancer and Duchenne Muscular Dystrophy.

The agency’s Center for Drug Evaluation and Research also provided funding through an agreement with NORD and the Critical Path Institute (C-Path) to develop a data platform to manage information on rare diseases. The Rare Disease Cures Accelerator — Data Analytics Platform (RDCA-DAP) will contain patient-level data from clinical trials, observational studies, patient registries, and real-world data such as electronic health records across a multitude of rare diseases.

NIH Makes Rare Disease Grants to Three Universities

NIH has awarded $7.8 million in grants to three universities conducting research on myasthenia gravis.

In addition to the funding, Yale University, George Washington University and Duke University will join the rare disease network for Myasthenia Gravis (MGNNet).

MGNNet, established under the NIH’s National Center for Advancing Translational Sciences, will add seven study sites to the 200 established at NIH rare disease research centers across the U.S.

UK Trials Still Underreported Despite Lawmaker Attempts

Clinical trial transparency problems continue in the UK despite warning letters to institutions that have failed to comply with the country’s legal mandate to report trial results.

A new report by nonprofit AllTrials found that fewer than nine percent of 151 trials
studied have posted all their trial results on the EU clinical trials register. More than 25 percent have failed to report any trial data at all.

The AllTrials study comes almost exactly a year after a report by the UK’s parliamentary Science and Technology Committee showed that only half of trials had reported their results within the required one year of the trial’s end (CenterWatch Weekly, Nov. 12, 2018).

A letter sent by the committee to non-compliant institutions in January warned that they had six months to improve their reporting. The committee, which has scheduled an Oct. 29 meeting to review the lack of progress, has urged the NHS Health and Research Authority to enforce rules and impose penalties on trial scofflaws.

Ken Getz’s New Edition of “The Gift of Participation” Released


The book focuses on the value of participation in clinical trials, what participation means for patients and how it can help advance science.

Practical information is included on subjects such as insurance coverage, compensation and tax ramifications for clinical research volunteers.

Additions to the book include:
- The role that social and digital media play in clinical research;
- The collection of biomarker data and genetic material in clinical research;
- Evolving rules on clinical trial results disclosure; and
- The patient engagement movement.

This feature highlights changes in clinical research organizations’ personnel.

**Accuray**  
Suzanne Winter has been appointed senior vice president and chief commercial officer at Accuray. Winter was formerly group vice president for the Americas region at Medtronic Diabetes.

**Achilles Therapeutics**  
Beverly Carr has been appointed chief business officer at Achilles Therapeutics. Carr was most recently vice president of business development for the immune-inflammation therapy area at GlaxoSmithKline.

**AMD Medicom**  
AMD Medicom named Guillaume Laverdure president of North America and Ouriel Levy executive vice president of commercial and global president of dental. Laverdure is currently chief operating officer at the company and will continue in that role. Levy is the former corporate vice president of sales for A.R. Medicom.

**AVROBIO**  
AVROBIO has appointed Holly May chief commercial officer. May was most recently vice president and head of commercial at SOBI.

**BlackThorn Therapeutics**  
BlackThorn Therapeutics has named William Martin chief executive officer. Martin most recently served as president and chief operating officer as well as the chief scientific officer of BlackThorn.

**Cadent Therapeutics**  
Cadent Therapeutics has appointed Christopher Kenney chief medical officer and Dawn Williams as vice president of clinical operations. Kenney last served as senior vice president of medical affairs at Acorda Therapeutics. Williams was most recently vice president of clinical operations and program management at Albireo Pharma.

**Caregiver**  
Beth Landry has been appointed the first chief operating officer at Caregiver. Landry previously served as senior vice president of operations at Seniorlink.

**Clinical Laserthermia Systems Americas**  
Micahel Magnani has been named managing director for the U.S. and North America at Clinical Laserthermia Systems Americas. Magnani previously served as the chief executive officer of StimAire.

**Harvard Bioscience**  
Ken Olson has been named vice president and general manager for pre-clinical systems at Harvard Bioscience. Olson was previously senior vice president of global engineering and operations at Spacelabs Healthcare.

**HepaRegeniX GmbH**  
HepaRegeniX GmbH has named Michael Lutz chief executive officer and managing director of the company. Lutz formerly served as CEO of LifeCodexx AG.

**Kintai Therapeutics**  
Kintai Therapeutics has appointed Francesca Barone head of experimental medicine. Barone was most recently a reader and academic head of business engagement for the college of medical and dental science at the University of Birmingham.

**LifeMine Therapeutics**  
Iain McFayden has been named chief data officer, Jared Cumming senior vice president and head of chemistry and Dawn Thompson vice president and head of microbiology and automation at LifeMine Therapeutics. Previously, McFayden served as head of computational sciences and next generation analytics at Moderna. Cumming most recently served as executive director of chemistry at Merck. Prior to joining LifeMine, Thompson was chief scientific officer at Directed Genomics.

**Lysogene**  
Stéphane Durant des Aulnois was named chief financial officer at Lysogene. Durant des Aulnois recently served as vice president and head of investor relations at the company.

**MediSpend**  
MediSpend has named Seth Houston chief commercial officer. Before joining the company, Houston served as managing director of IQVIA’s U.S. technology solutions business unit.

**Medtronic**  
Medtronic plc has named Sean Salmon executive vice president and group president of Medtronic Diabetes. Salmon was recently president of coronary and structural heart within the cardiac and vascular group at Medtronic.

**Moberg Pharma**  
Moberg Pharma has appointed Mark Beveridge as vice president of finance. Beveridge was most recently senior advisor in accounting for the company.

**Myriad Genetics**  
Myriad Genetics has named Mark Pollack chief medical officer of Myriad Neuroscience. Pollack served as a professor and chair of the department of psychiatry at Rush University Medical Center in Chicago and as a professor at Harvard Medical School’s center for anxiety and traumatic stress disorders.

**Novartis**  
Alice Shaw has been named lead of translational clinical oncology at Novartis. Shaw is a professor of medicine at Harvard Medical School and an attending physician in the Thoracic Cancer Program at Massachusetts General Hospital.

**On Target Laboratories**  
Kimberly Fabrizio has been appointed vice president of regulatory and quality at On Target Laboratories. Fabrizio previously held continues on next page »
Up and Coming (continued from page 4)

the position of vice president of regulatory affairs and compliance at Invicro.

Oncorus
John McCabe was named chief financial officer at Oncorus. Previously, McCabe was CEO of Flex Pharma, now known as Salarius Pharmaceuticals.

Pharmavite
Pharmavite has expanded its leadership team with the addition of Rhonda Hoffman as chief marketing officer. Hoffman previously served as CMO at Elanco Animal Health.

ReViral
Alan Musso has been named chief financial officer of ReViral. Musso was formerly CFO at Peloton Therapeutics.

Rheos Medicines
Rheos Medicines has named Barbara Fox chief executive officer. Fox was most recently CEO at Tilos Therapeutics.

Smith & Nephew
Roland Diggelmann has been named chief executive officer of Smith & Nephew. Diggelmann is the former CEO at Roche Diagnostics.

STALICLA
Stéphane Baudouin has been appointed chief of science at STALICLA. Baudouin was senior lecturer and team leader at Cardiff University.

Sumitomo Dainippon Pharma
Shigeyuki Nishinaka was named executive officer of global business development at Sumitomo Dainippon Pharma. Nishinaka previously held the position of executive officer of global business development and international business management at the company.

TLC
TLC has named Vincent Chang vice president of manufacturing and development. Chang was previously managing director of Yili Consulting, LLC.

Versameb AG
Versameb AG has named Isabel Ferreira chief business officer. Ferreira was previously with Roche where she served as director of global business and development.
Build Quality into Trials
continued from page 1

Build Quality into Trials
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a high-risk document requiring special handling, such as password protection. The SOP also could require a second person to sign off before distribution.

In “Randomization Schedule Disaster #2,” a CRO’s staff was directed to use randomized codes from a prior study to serve as dummy codes while the system was being set up. Under time pressure to activate the system, someone forgot to replace the dummy codes with authentic codes and patients were not randomized properly.

While the dummy codes may have looked identical to the actual randomized codes, Reinhard said, they were not. The dummy codes, if used at all, should have been altered to be obviously different from the real codes, for example by adding leading digits.

The system itself could have been identified as high risk, she said, and the SOP should have required a two-person sign-off procedure and included a checklist for review and release of the system.

The “Global Document ‘Version’ Catastrophe” involved a CRO hired to run a trial in 30 countries. Sites in five of the countries did not receive a third protocol amendment or the latest two versions of the informed consent form, which contained significant new safety information.

In that case, the problem was caused by a staffing issue. A trial administrator responsible for the five countries had to take an unanticipated medical leave, and the CRO didn’t find a replacement for two months. There was also no centralized monitoring of protocol signature pages or IRB approvals to detect the breakdown of communication.

Trials tend to run into difficulty in the hand-off of materials, Reinhard said. In this case, the CRO could have instituted a centralized monitoring of protocol signature pages or IRB approvals that would have caught the problem.

Reinhard recommends collecting informed consent data electronically so multiple ICFs can be tracked. Using real-time metrics on actual vs. anticipated ethics committee approvals also can help track risk at the country level.

In “The Case of the Delayed Interim Analysis,” Reinhard said, the planned interim analysis was delayed two months because database reconciliation with the trial’s electronic systems did not occur on schedule, causing numerous queries to be issued and reconciled. In addition, only eight of 20 investigators in the trial received training on the systems.

In that case, data management personnel had not adhered to the data management plan due to limited resources. The initial site activation checklist did not identify training requirements for investigators, and the pressure to go live and hit key checkpoints resulted in corners being cut.

Reinhard recommended identifying lack of data reconciliation and training as potential risks and requesting weekly and monthly status reports from all sources. She also suggested collecting metrics on the actual vs. anticipated number of investigators trained.

A vendor’s failure to report malfunctions led to trouble in “The Case of the ‘Missing’ Primary Endpoints.” A trial to test a pain measurement scale contracted an electronic patient-reported outcomes (ePRO) provider to collect post-surgical pain reports from 200 patients at specific time intervals. Site staff reported that the ePRO devices appeared to malfunction during use.

The ePRO provider, which did not track the number of actual vs. anticipated entries, disputed the reports without conducting further investigation. After the issue was escalated to the vendor’s management, it was revealed that 30 percent of the scores were missing, resulting in the need to increase enrollment.

The problem could have been avoided, Reinhard said, by designating the primary endpoint as a high-risk element of the trial, collecting real-time metrics on scores captured and performing periodic review of patient and staff queries about device function.

She also stressed that the trial’s managers should have proactively asked patients and sites about their experiences using the outsourced technology.

The lesson learned from all of these situations, Reinhard said, is that sites, CROs and sponsors should start their QBD efforts by performing a pre-trial risk analysis of processes and protocols to identify weak or overly complicated points. Once issues are spotted, fail-safe measures can be built in to avoid problems. Reinhard also recommended using metrics designed to pick up breakdowns in critical points early in the trial.

Most of all, she said, make sure that planning and kick-off meetings are more than a dog and pony show. Really dig into the details, she said, and “jump into how you will ‘operationalize’ the specific trial at hand.”
Giving Patients Back  
continued from page 1

for the latest version of our smartphones, Williams said.

Many trial participants feel like they are not really informed about a clinical trial and what they are consenting to. Being swiftly baptized into a clinical trial can leave the patient with a whirlwind of paperwork and the feeling that they don’t understand the science involved.

Rather than handing a patient a 20-page informed consent document full of long paragraphs and giving them only two minutes to read and sign it, patients should be guided and educated. This is where the concept of a nurse navigator can be helpful.

“Nurse navigators make a difference,” said cancer survivor Amy Joosten-Butler, who has participated in five clinical trials and is about to start her sixth. Joosten-Butler said her nurse navigator walked her through the informed consent document, distilling the information for her page by page.

Not all patients have the benefit of a guide, however. “I had to become a nuclear physicist to become an ambassador” for patients, said Kimberly Richardson, head of patient-centered outcomes in cancer research at the University of Chicago. “What regular person would do that? That’s an inherent barrier right off the bat, ‘Become us to be like us.’ That won’t work in patient advocacy.”

Patient engagement should go beyond the trial, experts and patients agreed. Too few trials share their end results with the participants.

Too often, results are only shared if they are successful,” said Seth Rotberg, Huntington’s Disease advocate and partnerships manager for Inspire. “Share it with the people who took the risk first,” Rotberg urged.

“I was lucky,” Williams said, noting that she lived in Manhattan, had a flexible work schedule and was treated by a Nobel Prize-winning scientist at a great hospital. “I know how to ask questions as a journalist as well. I had all of that and it was the scariest, most nail-biting, traumatic thing in the world.”

― Mary Elizabeth Williams

Patient Experiences Inform Trial Experts

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# Drug & Device Pipeline News

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<th>Company</th>
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<th>Status</th>
<th>Sponsor Contact</th>
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<tbody>
<tr>
<td>Cyclo Therapeutics, Inc.</td>
<td>Trappsol Cyclo</td>
<td>Niemann-Pick Disease Type C (NPC)</td>
<td>Phase 1 trial initiated enrolling 12 subjects with NPC age 18 years and older at UCSF Benioff Children's Hospital in Oakland, CA</td>
<td>cyclotherapeutics.com</td>
</tr>
<tr>
<td>Adverum Biotechnologies, Inc.</td>
<td>ADVM-022</td>
<td>wet age-related macular degeneration (wet AMD)</td>
<td>Phase 1 trial initiated enrolling subjects with wet AMD who are responsive to anti-vascular endothelial growth factor (VEGF) treatment at eight sites across the U.S.</td>
<td>adverum.com</td>
</tr>
<tr>
<td>Cerevel Therapeutics</td>
<td>CVL-231</td>
<td>schizophrenia</td>
<td>Phase 1b trial initiated enrolling 100 subjects age 18 to 50</td>
<td>cerevel.com</td>
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<tr>
<td>Axsome Therapeutics, Inc.</td>
<td>AXS-12</td>
<td>narcolepsy</td>
<td>Phase 2 trial initiated enrolling 100 subjects at multiple sites</td>
<td>axsome.com</td>
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<tr>
<td>ADC Therapeutics SA</td>
<td>ADCT-301 (camidanlumab tesirine)</td>
<td>relapsed or refractory Hodgkin lymphoma (HL)</td>
<td>Phase 2 trial initiated enrolling 100 subjects at multiple sites</td>
<td>adctherapeutics.com</td>
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<tr>
<td>Aristea Therapeutics</td>
<td>RIST4721</td>
<td>palmoplantar pustulosis (PPP)</td>
<td>Phase 2a trial initiated</td>
<td>aristeatx.com</td>
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<tr>
<td>HighTide Therapeutics, Inc.</td>
<td>HTD1801</td>
<td>nonalcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (T2DM)</td>
<td>Phase 2a trial initiated enrolling 100 subjects with NASH and T2DM at 17 sites in the U.S.</td>
<td>hightidetx.com</td>
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<tr>
<td>MacroGenics, Inc.</td>
<td>margetuximab</td>
<td>HER2-positive gastric cancer (GC) or gastroesophageal junction (GEJ) cancer</td>
<td>Phase 2/3 trial initiated enrolling subjects with HER2-positive and PD-L1-positive tumors at global sites</td>
<td>macrogenics.com</td>
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<tr>
<td>Myovant Sciences</td>
<td>relugolix combination therapy</td>
<td>endometriosis-associated pain</td>
<td>Phase 3 trial initiated enrolling 600 female subjects ages 18 to 50 at sites in the U.S.</td>
<td>myovant.com</td>
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<tr>
<td>Urovant Sciences, Inc.</td>
<td>Vibergron</td>
<td>overactive bladder (OAB)</td>
<td>Phase 3 (part 2) trial initiated enrolling 1,000 male subjects with OAB and benign prostatic hyperplasia (BPH)</td>
<td>urovant.com</td>
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<tr>
<td>Odontate Therapeutics, Inc.</td>
<td>tesetaxel</td>
<td>metastatic breast cancer</td>
<td>Phase 3 trial initiated enrolling 600 subjects with HER2 negative, hormone receptor positive metastatic breast cancer</td>
<td>odonate.com</td>
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<tr>
<td>FibroGen, Inc.</td>
<td>pamrevlumab</td>
<td>unresectable locally advanced pancreatic cancer (LAPC)</td>
<td>Phase 3 trial initiated enrolling 260 subjects</td>
<td>fibrogen.com</td>
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<td>Canon Medical Systems USA, Inc.</td>
<td>Advanced Intelligent Clear-IQ Engine (AiCE)</td>
<td>image reconstruction</td>
<td>510 (k) clearance granted by the FDA</td>
<td>us.medical.canon</td>
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<tr>
<td>Garwood Medical Devices</td>
<td>BioPrax</td>
<td>knee replacement</td>
<td>Breakthrough Device designation granted by the FDA</td>
<td>garwoodmedicaldevices.com</td>
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<td>CorFlow Therapeutics AG</td>
<td>CoFI (CorFlow Controlled Flow Infusion) System</td>
<td>coronary microcirculation after standard stent implantation</td>
<td>Breakthrough Device designation granted by the FDA</td>
<td>corflow-therapeutics.ch</td>
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For news on trial results, FDA approvals and drugs in development, Join the LinkedIn Drug Research Updates group!
### Drug & Device Pipeline News

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<td>acute myeloid leukemia</td>
<td>Fast track designation granted by the FDA</td>
<td>bergenbio.com</td>
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<td>Heron Therapeutics, Inc.</td>
<td>CINVANTI</td>
<td>prevention of acute and delayed chemotherapy-induced nausea</td>
<td>sNDA approval granted by the FDA</td>
<td>herontx.com</td>
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<td></td>
<td>(aprepitant)</td>
<td>and vomiting (CINV) following both highly emetogenic cancer</td>
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<td>injectable emulsion</td>
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<td>for intravenous</td>
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<td>Vertex Pharmaceuticals Inc.</td>
<td>Trikafta</td>
<td>cystic fibrosis</td>
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<td>vrtx.com</td>
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<td>Novartis</td>
<td>Beovu</td>
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<td>Approval granted by the FDA</td>
<td>novartis.com</td>
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<td>AstraZeneca</td>
<td>Farxiga</td>
<td>type 2 diabetes</td>
<td>Approval granted by the FDA</td>
<td>astrazeneca-us.com</td>
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<td>AstraZeneca</td>
<td>(dolagliflozin)</td>
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<td>Alexion Pharmaceuticals, Inc.</td>
<td>ULTOMIRIS</td>
<td>atypical hemolytic uremic syndrome (aHUS)</td>
<td>Approval granted by the FDA</td>
<td>alexion.com</td>
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<td>Janssen</td>
<td>Stelara</td>
<td>moderately to severely active ulcerative colitis</td>
<td>Approval granted by the FDA</td>
<td>janssen.com</td>
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<td>Foamix Pharmaceuticals, Ltd.</td>
<td>AMZEEQ</td>
<td>moderate to severe acne vulgaris</td>
<td>Approval granted by the FDA</td>
<td>foamix.com</td>
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<tr>
<td>Eton Pharmaceuticals, Inc.</td>
<td>Biorphen</td>
<td>hypotension during anesthesia</td>
<td>Approval granted by the FDA</td>
<td>etonpharma.com</td>
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<tr>
<td></td>
<td>(phenylephrine)</td>
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### STANDARD OPERATING PROCEDURES

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This collection of 26 SOPs is easily customized to match your culture and internal processes. Highlights include:

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- Protocol compliance
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- Protecting confidential information
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Click on any provider to view the company’s complete online profile or click here to search more profiles.

### CONTRACT RESEARCH ORGANIZATIONS

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<th>Company Name</th>
<th>Location</th>
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<tbody>
<tr>
<td>Confidence Pharmaceutical Research</td>
<td>Burlington, CA</td>
<td>(401) 965-3377</td>
<td><a href="mailto:anna.ravdel@confidenceresearch.com">anna.ravdel@confidenceresearch.com</a></td>
</tr>
<tr>
<td>CROMSOURCE</td>
<td>Waltham, MA</td>
<td>(617) 871-1128</td>
<td><a href="mailto:april.mccall@cromsource.com">april.mccall@cromsource.com</a></td>
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<tr>
<td>Lotus Clinical Research, LLC</td>
<td>Pasadena, CA</td>
<td>(626) 568-8727</td>
<td>generallotuscr.com</td>
</tr>
<tr>
<td>Pivotal S.L.</td>
<td>Madrid, Spain</td>
<td>0034 679 488 022</td>
<td><a href="mailto:bd@pivotal.es">bd@pivotal.es</a></td>
</tr>
<tr>
<td>Promedica International</td>
<td>Costa Mesa, CA</td>
<td>(714) 460-7363 Ext. 17</td>
<td><a href="mailto:thopton@promedica-intl.com">thopton@promedica-intl.com</a></td>
</tr>
<tr>
<td>Virtrial</td>
<td>Scottsdale, AZ</td>
<td>(480) 462-2222</td>
<td><a href="mailto:kimkundert@virtrial.com">kimkundert@virtrial.com</a></td>
</tr>
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</table>

Confidence Pharmaceutical Research is a CRO and a vendor management organization that helps clinical trial sponsors run better trials. Our focus is on transparency, reducing waste and producing rigorous metrics.

CROMSOURCE was among the first CROs to become active in Central & Eastern Europe and Russia. Their successful growth has been built on stability, integrity, high levels of customer satisfaction and repeated business.

Since 2001, Lotus has honed its study design and conduct methodology, interacts on behalf of clients with the FDA’s Analgesics Division and understands how to efficiently navigate the agency’s regulatory framework.

Pivotal was founded in 2001 by Dr. Ibrahim Farr on the principle that strategic medical advice and support should be the backbone of all clinical trials. Pivotal currently employs 200 cross-functional professionals.

More than two decades of experience shapes PMI’s understanding of the many clinical and regulatory challenges facing healthcare providers and the healthcare industry today.

### INSTITUTIONAL REVIEW BOARD

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<th>Email Address</th>
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<tbody>
<tr>
<td>Biomedical Research Alliance of New York, LLC</td>
<td>Lake Success, NY</td>
<td>(516) 470-6900</td>
<td><a href="mailto:info@brany.com">info@brany.com</a></td>
</tr>
<tr>
<td>PMG Research, Inc.</td>
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<td><a href="mailto:kcole@pmg-research.com">kcole@pmg-research.com</a></td>
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BRANY provides IRB administration for more than 1,100 active research trials. It coordinates the study start-up process and manages study start-up and research revenue tracking through study closeout.

PMG Research is an Integrated Site Network (ISN) of 12 clinical research facilities. Since its founding in 1979, PMG has conducted over 7,700 research studies.

### INVESTIGATIVE SITE NETWORK

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<tbody>
<tr>
<td>Wake Research Associates</td>
<td>Raleigh, NC</td>
<td>(919) 781-2514</td>
<td><a href="mailto:contactus@wakeresearch.com">contactus@wakeresearch.com</a></td>
</tr>
<tr>
<td>Complion</td>
<td>Cleveland, OH</td>
<td>(800) 615-9077</td>
<td><a href="mailto:contact@complion.com">contact@complion.com</a></td>
</tr>
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</table>

Wake Research Associates, established in 1984, is a nationally recognized professional research organization specializing in conducting pharmaceutical, device and nutrition trials.

Leading sites, hospitals, academic medical centers, health systems and cancer centers around the country use Complion to go paperless, improve compliance and streamline operations.

### SITE CONSORTIUM

### TECHNOLOGY SOLUTIONS

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Virtrial offers a patient management program that combines live video, text and email for clinical trial sites to easily, efficiently and conveniently address specific patient and/or study needs.