Broden Criteria to Maximize Trial Results, FDA Says
By Leslie Ramsey

Sponsors should think about loosening their exclusion criteria to allow more diverse patient populations — especially when recruiting for later stage trials, the FDA says in new draft guidance published last week.

The agency says that part of the low recruitment problem may be that sponsors are stuck on finding patients who only suffer from a given disease and no others. Perhaps worse, they exclude populations such as elders, kids, obese (or overly thin) patients, and HIV-positive patients.

“For example, if there are unreasonable risks to participants with advanced heart failure, but enrollment of those with a milder disease would be appropriate, the exclusion criteria should specifically define the population of heart failure participants that should be excluded,” the agency said in the 18-page document.

This is especially true of Phase II trials as they tend to be more restrictive. Sponsors should consider eliminating or modifying certain criteria when they move to Phase III.

For trials focused on rare diseases or conditions, the FDA advises sponsors to consider engaging with patient advocacy groups early in the process, planning to re-enroll participants from early-phase trials into later-phase trials and conducting open-label extension studies to ensure that all study participants will have access to the investigational treatment.

The agency offers several examples of trial design and methodologies to broaden see Broden Criteria on page 5

By John Mitchell

Clinical trials can’t focus on everything when it comes to process improvement, so sponsors and sites need to focus on critical success factors, such as data reliability and protecting subjects.

Sponsors need to follow data end-to-end, from subject to final database, and look for weak spots, said Keith Dorrict of Dorrict Metrics and Process Improvement at a WCG-sponsored webinar. Think about, for example, what processes data go through, whether vendors or subcontractors are involved, and whether there is any data transfer.

Once critical success factors are defined, said Linda Sullivan, president of Metrics Champion Consortium (MCC), you need to identify key performance questions for each factor to tell you whether you are on track to achieve those success factors.

It’s often a challenge to decide what level of metrics you need to analyze, Dorrict said. He noted four basic levels:

- Portfolio — Measures across multiple studies, which are useful for vendor oversight;
- Study — Measures across a single study, which also are useful for drill-down of portfolio-level metrics;
- Country — Measures across a country, which are useful for oversight of country-specific challenges and drill-down of study-level results; and
- Investigative Site — Measures site performance against a target or compares against other sites in the same country or study.

see Managing Risk on page 5
FDA Advises on Phase III Trials for NASH with Symptom-Free Cirrhosis

The FDA last week issued a draft guidance on Phase III trials of treatments for nonalcoholic steatohepatitis (NASH) with symptom-free cirrhosis, including recommendations on enrollment criteria, trial design, efficacy endpoints and safety considerations.

The draft guidance says sponsors should enroll only patients whose cirrhosis is secondary to NASH, using histological criteria. The agency also will accept non-histological criteria if they are scientifically supported.

Sponsors should consider using endpoints such as complication of ascites, variceal hemorrhage, hepatic encephalopathy, worsening of condition to the point of requiring liver transplant or death from any cause.

In addition, the trial protocol should specify criteria for excluding patients with decompensated cirrhosis — where the cirrhosis has progressed and the liver is no longer fully functioning. Sponsors should not enroll patients listed for liver transplantation, the agency says.


NIH Lays Out $42M for Genomic Medicine Trials

The NIH will pay up to $42 million over the next five years for clinical trials on whether genomic medicine can help people with chronic diseases manage their care better.

The trials, scheduled to begin next year, represent the second phase of the agency’s Implementing Genomics in Practice (IGNITE) Network. The first trial will examine whether early access to patients’ genomic data will help them manage high blood pressure, hypertension and kidney disease.

The second trial will focus on pain and depression. It “seeks to test whether patients with acute post-surgical pain, chronic pain and depression have better clinical outcomes if pharmacogenomics guide opioid and antidepressant prescriptions.”

The trials will be held at sites at the Universities of Florida and Indiana, Duke, Vanderbilt and the Icahn School of Medicine at Mount Sinai.

New Data Tool Available to Medical Device Sponsors

Medical device sponsors now can access a data-driven benchmarking program to help accelerate study start-up.

WCG’s KMR Group has opened its Site Contracts Program to medical device companies for the first time, the company announced. Already in use by biopharma companies, the program has helped reduce trial start-up time by up to 20 percent and decrease costs by 15 percent.

“This program will give device companies a rock-solid foundation of proprietary, independently verified data on which to build their study plans and implement performance improvements, as well as unique evidence-based insights to guide their decision-making,” says KMR president and founder Linda Martin.

Emerging Biotechs Lead the Way in 2018, Report Says

The number of active clinical-stage programs reached a record 6,984 in 2018, the Biotechnology Innovation Organization (BIO) says in a new report, with emerging biotech companies accounting for 73% of these programs.

BIO found that 45 percent of emerging companies partnered with other companies to pursue their pipelines. Half of oncology studies are being conducted by such partnerships, and 36 percent of cardiovascular and infectious disease studies are partnered.

The U.S. leads the world in the number of emerging companies entering the

More than 870,000 patients were enrolled in English clinical research studies in the past 12 months, an increase of 140,000 over the previous 12-month period. Nearly 2,400 subjects per day were involved in a clinical trial, NIHR says.

And participation rates continue to grow year by year. The number of participants recruited for NIHR-supported studies annually has hit record levels for the past three years, with the 2018-2019 growth rate coming in at the highest ever, 20 percent.

Most patients this year were enrolled in children’s studies (81,892), followed by studies in primary care settings (78,533), reproductive health and childbirth (74,128), cancer (67,652) and mental health (65,645), the NIHR says.
pipeline, with 44 percent, compared to 17 percent in Europe and 8 percent in Asia. Read the report here: https://bit.ly/2WNoh1L.

**Study Finds Lack of Faith in Randomized Testing**

Evidence-based research faces a challenge, according to one study that indicates a negative public view of comparison testing. A study conducted by researchers at the Geisinger Health System’s Center for Translational Bioethics and Healthcare Policy found evidence that A/B tests comparing the effectiveness of two treatments, practices or policies often are criticized as inappropriate despite people finding the untested implementation of A or B to be appropriate.

Researchers examined 16 studies from sectors ranging from healthcare to public policy that involved 5,873 participants from three populations. Even when each of the options being compared are themselves unobjectionable, participants expressed disapproval of testing to prove superiority of one over the other.

Although participants’ reactions may be largely due to unfamiliarity with scientific methods, the study says, negative public perception may tend to lead researchers and policymakers away from randomized testing and may make it more difficult to recruit subjects.

Thorough evaluation of treatments through randomized trials could cause greater opposition than simply implementing them without proper testing, the researchers conclude.

Read the report at: https://bit.ly/2I13uOQ.

**Evidera to Acquire RWE Company Medimix**

Evidera, a business unit of PPD, will acquire real-world evidence data company Medimix International, the company announced last month.

The Medimix database, which includes 2.2 million clinicians in more than 60 countries, will support Evidera’s mission to provide evidence-based solutions that demonstrate the effectiveness, safety and value of healthcare products.

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Up and Coming

This feature highlights changes in clinical research companies’ personnel.

**Bristol-Myers Squibb**
Following the completion of the purchase of Celgene, Bristol-Myers Squibb has announced that the company will restructure around two core areas—research and early development (R&ED) and global drug development. Rupert Vessey, who currently serves as president of R&ED at Celgene, will assume the same role at the combined company. Samat Hirawat, current head of oncology development at Novartis, will join the combined company as chief medical officer for global drug development. Chris Boerner will continue in his role as chief commercialization officer, and Nadim Ahmed, current president of global hematology and oncology at Celgene, will serve as president of hematology, to include cell therapy, at the combined company. David Elkins, who is currently chief financial officer of Celgene, will have the same role at the merged drugmaker.

**Sanofi**
Sanofi has announced the appointment of Paul Hudson as CEO. Hudson was previously head of Novartis’ pharmaceuticals division. Current CEO Olivier Brandicourt will retire September 1.

**Novartis**
Marie-France Tschudin has been named president of Novartis’ pharmaceuticals division. Tschudin is currently the president of the advanced accelerator applications company at Novartis.

**Gilead**
Johanna Mercier has been named commercial chief at Gilead, effective July 1. Mercier is currently the president of U.S. and large markets at Bristol Myers-Squibb.

**Atara**
T cell-focused biotech Atara has named Pascal Touchon as president and CEO of the company. Touchon was previously the head of oncology and global head of the cell and gene therapy unit at Novartis. Atara’s global head of R&D, Dietmar Berger, has resigned from the company to join Sanofi as head of development.

**Audentes Therapeutics**
San Francisco-based Audentes Therapeutics has appointed Edward R. Conner as senior vice president and chief medical officer, replacing Suyash Prasad. Conner was previously at Sangamo Therapeutics, where he led the clinical development of the company’s pipeline of genomic therapeutics. Fulvio Mavilio will move up to senior vice president of translational science. The appointments will be effective July 15. The company has announced the departure John Gray, current senior vice president and chief technology officer.

**Theravance**
Theravance Biopharma has named Andrew Hindman as senior vice president and chief financial officer. Hindman has held several senior executive-level positions in the biopharmaceutical industry, most recently as chief business officer of Acorda Therapeutics.

**LabCorp**
Adam Schechter has been named CEO and president of LabCorp as David King is set to retire October 31. Schechter, a longtime Merck executive, is currently the president of global human health.

**Casebia Therapeutics**
Stephen Kennedy has been named as senior vice president and head of technical operations at Casebia Therapeutics. Kennedy formerly served as vice president and head, and general manager – Japan. Sugita most recently served as vice president and head, regional leader of the integrated team for medical, clinical and regulatory in Asia/Pacific medical devices at Johnson & Johnson.

**Dicerna**
Dicerna Pharmaceuticals has announced the appointment of Rob Ciappenelli as chief commercial officer. Ciappenelli most recently held leadership roles at Momenta Pharmaceuticals, Shire Pharmaceuticals and Sunovion Pharmaceuticals.

**Eisai**
Eisai, Inc., the U.S. pharmaceutical subsidiary of Eisai Co., Ltd., has announced the immediate appointment of Patrick Coyle as vice president and chief financial officer. Coyle was formerly vice president of financial planning and analysis at INSMED Inc.

**Pfizer**
Pfizer has named Jeff Settleman senior vice president and group head of oncology research and development, effective July 1. Settleman was head of oncology research at Calico Life Sciences.

**AGC Biologics**
Kasper Møller has been appointed chief technical officer at AGC Biologics. Møller has held various roles over twelve years at AGC Biologics, most recently as the site head for Copenhagen.

**BIO**
Rich Masters has been named executive vice president for public affairs at BIO, effective June 17. Masters previously held a position at Qorvis Communications.

**Parexel**
Parexel has announced the appointment of Makoto Sugita as senior vice president and general manager – Japan. Sugita most recently served as vice president and head, regional leader of the integrated team for medical, clinical and regulatory at AGC Biologics.

**LEO Pharma**
LEO Pharma has announced the appointment of Catherine Mazzacco as president and CEO, effective August 1. Mazzacco is currently the head of global commercial operations at GE Healthcare’s BioPharma division.

**Immunovant**
Immunovant has named Pete Salzmann, M.D., as CEO. Salzmann was most recently global clinical development leader for Eli Lilly’s recently approved Rheumatoid Arthritis drug, Olumiant.
Features

Broaden Criteria
continued from page 1

inclusion, including adaptive clinical trials, expansion cohorts that allow for dose modification in specific populations, the creation of pediatric development programs that stagger enrollment based on age and the inclusion of a broader participant group as part of the secondary efficacy and safety analyses.

The document also offers several recommendations for enrollment and retention practices that enhance inclusiveness, including working with communities to address participant needs and gather valuable insights for trial design, and holding frequent recruitment events in nonclinical settings.

Part of the low recruitment problem may be that sponsors are stuck on finding patients who only suffer from a given disease and no others.

Managing Risk
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Sullivan likened metrics-based risk management to a three-legged stool: trial success is the seat propped up by the legs of time, cost and quality. All three legs matter, she says. Too often, metrics focus on just one and neglect the others, unbalancing the stool.

“What you measure sends a signal about what you think is important, and it does, in fact, influence behavior,” Sullivan said. “Using a balanced set of metrics provides those incentives for people to behave the way you want them to.”

For more information on metrics and risk management, register for MCC’s Clinical Trial Risk and Performance Management Summit scheduled for September 4-5 in Philadelphia.

Listen to the entire webinar here: https://bit.ly/2QX1XNR.

“Sponsors need to follow data end-to-end, from subject to final database, and look for weak spots.”

— Keith Dorricott, Dorricott Metrics and Process Improvement

After much discussion and repeated postponements, the updated Common Rule finally took effect on January 21, 2019.

In The Revised Common Rule report two prominent healthcare attorneys sift through the new rule to mark out every deletion—highlight every addition—interpret every rewording—that clinical research professionals and institutions will need to understand to be ready to comply.

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<tr>
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<th>Medical Condition</th>
<th>Status</th>
<th>Sponsor Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celldex Therapeutics, Inc.</td>
<td>CK0801</td>
<td>bone marrow failure syndromes, including aplastic anemia, hypoplastic myelodysplasia and primary myelofibrosis</td>
<td>Phase I trial initiated</td>
<td>cellenkosinc.com</td>
</tr>
<tr>
<td>Xencor, Inc.</td>
<td>XmAb22841</td>
<td>advanced solid tumors</td>
<td>Phase I trial initiated</td>
<td>xencor.com</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals, Inc.</td>
<td>ALN-AGT</td>
<td>hypertension</td>
<td>Phase I trial initiated enrolling 168 subjects</td>
<td>alnylam.com</td>
</tr>
<tr>
<td>UCB</td>
<td>UCB0599</td>
<td>Parkinson’s disease</td>
<td>Phase II trial initiated</td>
<td>ucb.com</td>
</tr>
<tr>
<td>Amphera B.V.</td>
<td>MesoPher</td>
<td>pancreatic cancer</td>
<td>Phase II trial initiated enrolling 10 adult subjects with surgically resected pancreatic cancer who have received adjuvant standard of care treatment</td>
<td>amphera.nl</td>
</tr>
<tr>
<td>Immunovant</td>
<td>IMVT-1401</td>
<td>moderate-to-severe active Graves’ ophthalmopathy (GO)</td>
<td>Phase II trial initiated enrolling eight subjects</td>
<td>immunovant.com</td>
</tr>
<tr>
<td>Rejenevie Therapeutics</td>
<td>AR-100</td>
<td>immune restoration therapy</td>
<td>Phase II trial initiated enrolling 20 healthy subjects 55 years of age or older in Freeport, Bahamas</td>
<td>rejenevie.com</td>
</tr>
<tr>
<td>Ironwood Pharmaceuticals, Inc.</td>
<td>MD-7246</td>
<td>abdominal pain associated with irritable bowel syndrome with diarrhea (IBS-D)</td>
<td>Phase II trial initiated enrolling 400 subjects</td>
<td>ironwoodpharma.com</td>
</tr>
<tr>
<td>Verona Pharma PLC</td>
<td>RPL554</td>
<td>metered-dose inhaler formulation of ensifentrine (RPL554)</td>
<td>Phase II trial initiated enrolling 36 subjects at two sites in the UK</td>
<td>veronapharma.com</td>
</tr>
<tr>
<td>Minoryx Therapeutics</td>
<td>MIN-102</td>
<td>Friedreich's Ataxia</td>
<td>Phase II trial initiated enrolling 36 subjects 12 years of age or older at numerous sites across Europe</td>
<td>minoryx.com</td>
</tr>
<tr>
<td>GEFIT</td>
<td>elafibranor</td>
<td>nonalcoholic fatty liver disease (NAFLD)</td>
<td>Phase II trial initiated enrolling 16 subjects with NAFL as identified with magnetic resonance spectroscopy (H-MRS)</td>
<td>genfit.com</td>
</tr>
<tr>
<td>Arcutis, Inc.</td>
<td>ARQ-151</td>
<td>atopic dermatitis</td>
<td>Phase IIa trial initiated</td>
<td>arcutis.com</td>
</tr>
<tr>
<td>Akero Therapeutics, Inc.</td>
<td>AKR-001</td>
<td>non-alcoholic steatohepatitis (NASH)</td>
<td>Phase IIa trial initiated enrolling 80 subjects</td>
<td>akerotx.com</td>
</tr>
<tr>
<td>Ansun Biopharma, Inc.</td>
<td>DAS181</td>
<td>lower respiratory tract parainfluenza virus</td>
<td>Phase III trial initiated enrolling immunocompromised subjects at sites in the U.S., Europe and Asia</td>
<td>ansunbiopharma.com</td>
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</table>
### Drug & Device Pipeline News

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<table>
<thead>
<tr>
<th>Company</th>
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<th>Status</th>
<th>Sponsor Contact</th>
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<tr>
<td>Eyenovia Inc.</td>
<td>MicroPine</td>
<td>pediatric progressive myopia</td>
<td>Phase III trial initiated enrolling 400 subjects ages three to 12 years of age</td>
<td>eyenovia.com</td>
</tr>
<tr>
<td>Incyte</td>
<td>pemigatinib (INCB54828)</td>
<td>cholangiocarcinoma</td>
<td>Phase III trial initiated enrolling 432 subjects</td>
<td>incyte.com</td>
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<tr>
<td>Allergan plc, Gedeon Richter PLC</td>
<td>VRAYLAR (cariprazine)</td>
<td>manic or mixed episodes associated with bipolar I disorder in adults</td>
<td>sNDA approval granted by the FDA</td>
<td>allergan.com, richter.hu</td>
</tr>
<tr>
<td>Cadent Therapeutics</td>
<td>CAD-1883</td>
<td>spinocerebellar ataxia (SCA)</td>
<td>Orphan Drug designation granted by the FDA</td>
<td>cadenttx.com</td>
</tr>
<tr>
<td>Bayer</td>
<td>Aliqopa (copanlisib)</td>
<td>marginal zone lymphoma (MZL)</td>
<td>Breakthrough Therapy designation granted by the FDA</td>
<td>bayer.com</td>
</tr>
<tr>
<td>Imara, Inc.</td>
<td>IMR-687</td>
<td>sickle cell disease</td>
<td>Fast Track designation granted by the FDA</td>
<td>imaratx.com</td>
</tr>
<tr>
<td>NovoCure</td>
<td>NovoTTF-100L System in combination with pemetrexed plus platinum-based chemotherapy</td>
<td>malignant pleural mesothelioma (MPM)</td>
<td>Approval granted by the FDA</td>
<td>novocure.com</td>
</tr>
<tr>
<td>AveXis Inc.</td>
<td>Zolgensma (onasemnogene abeparvovec-xioi)</td>
<td>spinal muscular atrophy (SMA) in children less than two years of age</td>
<td>Approval granted by the FDA</td>
<td>avexis.com</td>
</tr>
<tr>
<td>Novartis</td>
<td>Piqray (alpelisib)</td>
<td>hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced or metastatic breast cancer in postmenopausal women and men</td>
<td>Approval granted by the FDA</td>
<td>novartis.com</td>
</tr>
<tr>
<td>Novartis</td>
<td>Jakafi (ruxolitinib)</td>
<td>steroid-refractory acute GVHD in adult and pediatric subjects 12 years and older</td>
<td>Approval granted by the FDA</td>
<td>novartis.com</td>
</tr>
<tr>
<td>Celgene Corporation</td>
<td>REVLIMID (lenalidomide) in combination with a rituximab product (R²)</td>
<td>previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL) in adults</td>
<td>Approval granted by the FDA</td>
<td>celgene.com</td>
</tr>
</tbody>
</table>

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