CenterWatch Weekly

March 15, 2021

COVID-19 Update…2
Industry Briefs…5
FCRI Update…6
Up and Coming…7
Drug & Device Pipeline News…11
Thirty-six drugs and devices have entered a new trial phase this week.
JobWatch…13

Increasing Protocol Complexity Requires Adapting Quality Metrics Tools

By Charlie Passut

The issue of protocol complexity is receiving increased attention with the release of new data that show dramatic growth in the number of trial endpoints, data points and amendments, and industry stakeholders are mobilizing to adapt management and metrics tools to keep up.

With this data in mind — as well as the imminent release of the International Council on Harmonization's (ICH) revised quality management guideline, ICH E8 — industry groups have begun the hard work of revising their quality metrics standards.

"We're going to have to change the way we look at, measure and define many of our metrics moving forward," says Ken Getz, director of the Tufts Center for the Study of Drug Development (CSDD). "It's really keeping us on our toes as we continue to adapt our designs and the development pathway." Getz presented data from CSDD's most recent analysis of protocol complexity metrics last week to members of the WCG Metrics Champion Consortium (MCC) working group on risk management and quality improvement.

The time is right to update our approach to managing protocol complexity, says MCC founder and CEO Linda Sullivan. MCC is working on revising its protocol complexity and cost evaluation tools, which help sites cope with the extra burden unwieldy protocols and amendments create.

see **Increasing Protocol Complexity** on page 8 »

Ask the Experts: Participant Reimbursement, Compensation and Incentives

This monthly feature presents a variety of questions from clinical trial professionals with answers from WCG Clinical's expert staff. This month features Yvonne Higgins, WCG IRB quality assurance adviser, and David Borasky, vice president of IRB compliance.

Question: *As a sponsor, what do the regulations say about paying research subjects? What are acceptable practices for compensating subjects for participating in a clinical trial?*

Answer: The FDA's and other federal regulations on human subject protections do not specifically address payment. The regulations do require that informed consent must be obtained under circumstances "that minimize the possibility of coercion or undue influence." The Office for Human Research Protections (OHRP) guidance states: "Paying research subjects is a common, and in general, acceptable practice."

In fact, it is common for subjects to be paid for their participation in research. Sponsors, researchers and IRBs may consider the following as acceptable practices for compensating subjects.

1. **Reimbursement of Study-Related Expenses** Research participation should be cost-neutral. This helps to ensure the principle of distributive justice and that the risks and benefits of research participation are fairly distributed. A number of different models for covering out-of-pocket expenses are acceptable, including collection of

see **Ask the Experts** on page 9 »

COVID-19 Update

COVID-19 Drug Research Roundup

COVID-19 Therapies:

Merck's ivermectin product Stromectol did not improve the rate of recovery better than placebo in patients with mild COVID-19, according to findings from a randomized clinical trial. The study included 476 patients who were enrolled at a single site in Columbia. Treatment with ivermectin in this trial led to symptom resolution after a median of 10 days vs. 12 days in the placebo group. Approximately 82 percent of patients in the ivermectin arm and 79 percent of participants in the placebo group experienced symptom resolution by day 21. Multiorgan failure was the most common serious adverse event, which occurred in two patients in each arm.

Ridgeback Biotherapeutics' and **Merck's** co-developed experimental antiviral candidate MK-4482 (molnupiravir) significantly reduced COVID-19 infection after five days in a multicenter, phase 2a trial. The trial included 202 nonhospitalized patients with SARS-CoV-2 infection. None of the patients who received molnupiravir had a positive COVID-19 test result after five days, while 24 percent of patients in the placebo group still had a positive test result for the novel coronavirus. Patients treated early in the course of their disease also experienced a faster reduction in infectious virus if they were treated with molnupiravir. Merck says it is currently planning to launch a phase 3 study to evaluate MK-7110 (CD24Fc), a Merck-acquired investigational COVID-19 agent, to support data from another study that didn't have enough participants to support an Emergency Use Authorization or approval.

The ongoing UK-based RECOVERY trial has halted enrollment of patients in a treatment arm evaluating the anti-inflammatory gout drug colchicine. Researchers added the colchicine arm to the trial last year after it showed potential in previous research for the management of severely ill hospitalized patients with COVID-19 who required mechanical ventilation. Enrollment was halted after an independent data monitoring committee found the drug provided no clinical benefit in a review of efficacy data that involved 11,162 patients. Colchicine ultimately had no significant benefit on 28-day mortality compared with standard of care in this patient population. The RECOVERY trial will continue to enroll for other trial arms, including those evaluating **Roche's** arthritis agent Actemra (tocilizumab), **Regeneron's** antibody cocktail comprising casirivimab and imdevimab, as well as dimethyl fumarate and aspirin.

Phase 2 and 3 trials show **Eli Lilly's** monoclonal antibody bamlanivimab reduces viral load and symptoms of COVID-19 and also reduces COVID-19-related hospitalizations by up to 70 percent. A combination regimen consisting of bamlanivimab and Lilly's etesevimab also reduced COVID-19-related hospitalizations and death by 70 percent in high-risk patients and those with mild-to-moderate COVID-19. Based on these data, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended Lilly's monoclonal antibodies as potential COVID-19 treatments. This positive recommendation will likely influence the European Commission to authorize the use of the antibodies for COVID-19.

The late stage of the National Institutes of Health's (NIH) ACTIV-3 trial will not evaluate **Brii Biosciences'** investigational monoclonal antibodies BRII-196 and BRII-198 after a trial found the two agents did not reach the minimum required efficacy rate for hospitalized COVID-19 patients. The decision was made to not move forward with BRII-196 and BRII-198 based on an evaluation of safety and efficacy for the combined antibodies in 150 hospitalized patients with COVID-19. Brii's BRII-196 and BRII-198 are both derived from the plasma of patients who have recovered from COVID-19. While NIH will not move forward with evaluating these agents, Brii says it will continue to evaluate the antibody combination in ambulatory patients with COVID-19.

The NIH has launched another ACTIV-4 phase 3 trial that is focusing on the use of blood thinners to prevent life-threatening blood clots in discharged patients with moderate-to-severe COVID-19. The first patient was enrolled in the trial on Feb. 15. The trial will first focus on the use of **Bristol Myers Squibb/Pfizer's** blood thinner Eliquis® (apixaban) in discharged patients with a diagnosis of moderate-to-severe COVID-19. Researchers of the trial will evaluate whether patients randomized to apixaban experience a lower rate of any thrombotic complication within 45 days compared with patients randomized to placebo. To date, the ACTIV-4 adaptive clinical trials are being conducted at more than 100 sites across the globe.

A phase 3 trial has found that **CytoDyn's** CCR5 antagonist candidate Vyrologix (leronlimab) improved survival and reduced hospital stay in critically ill hospitalized patients with COVID-19. Treatment with leronlimab in this trial led to a 24 percent reduction in all-cause mortality compared with placebo. Additionally, patients treated with leronlimab had a six-day shorter hospital stay compared with those who received placebo. Overall, patients who received leronlimab had a 166 percent better improvement in their probability of being alive at discharge by day 28. CytoDyn says it has reported the trial data to the FDA and the UK's Medicines and Healthcare product Regulatory Agency as well as Health Canada to see what next steps are necessary to ensure ultimate approval for the therapy in COVID-19. The company has also filed an additional protocol with the FDA to include more patients with severe COVID-19 at existing study sites.

A newly launched pilot study is testing the safety of a combination of 13 traditional

continues on next page »

COVID-19 Update

(continued from page 2)

Chinese medicinal compounds in patients with COVID-19. These compounds were used early during the COVID-19 pandemic, but large-scale research has yet to confirm their safety or efficacy for fighting the novel coronavirus. Researchers from the University of Southern California are spearheading the pilot study, which will examine the use of Xuanfei Baidu granules in mild-to-moderate COVID-19. The 12-week, placebo-controlled study is fully remote. Investigators will remotely obtain informed consent and monitor patient performance. Data generated from this study should inform the design of larger phase 2 studies evaluating the traditional Chinese medicinal compounds.

A multicenter, open-label clinical trial has shown that treatment with **Viriom's** and **Chromis'** Avifavir (favipiravir) was associated with a significantly shorter time to elimination of the COVID-19 virus compared with standard of care in hospitalized patients with medium-severe-to-severe COVID-19. In the trial, a total of 470 patients were randomized to receive either favipiravir or standard of care. Researchers found that the median time to clinical improvement was also significantly shorter in the favipiravir arm (12 vs. 15 days). The mortality rate was also proportionally smaller at 5.7 percent in the favipiravir group vs. 8.3 percent in the standard of care group. Overall, the treatment was well-tolerated.

An interim analysis of the phase 3 COMET-ICE trial shows that treatment with monoclonal antibody VIR-7831 (GSK4182136) from **Vir Biotechnology** and **GlaxoSmithKline (GSK)** led to an 85 percent reduction in hospitalization or death when given early in patients with COVID-19. The trial is ongoing, and patients are continuing to be followed for up to 24 weeks. Given the positive findings from this trial, both Vir and GSK say they plan to submit an Emergency Use Authorization to the FDA for the drug. The global phase 3 portion of the COMET-ICE trial is currently evaluating the safety and efficacy of a single VIR-7831 infusion vs. placebo in up to 1,300 nonhospitalized participants with COVID-19.

COVID-19 Vaccines:

A laboratory study of 20 serum samples from 15 patients with COVID-19 suggests the **Pfizer/BioNTech** COVID-19 vaccine is effective against the emerging Brazilian SARS-CoV-2 variant. The study, conducted at the University of Texas Medical Branch, used serum samples from patients in the companies' late-stage vaccine trial. According to the findings, the two-dose vaccine generated neutralization against both the Brazilian and UK strains that was similar to that seen against the original SARS-CoV-2 virus. Robust neutralization was also observed against the South African variant but at a lower rate than against the other variants. Since the study was conducted in a lab, researchers are still unsure how well the findings may generalize to the real-world setting.

Meanwhile, **Pfizer** announced it will enroll up to 4,000 healthy pregnant adult women in placebo-controlled COVID-19 vaccine trials to study if the vaccine is safe and effective in this population. Only women who are 24 to 34 weeks into their pregnancy will be eligible for enrollment. In addition to safety and efficacy assessments, researchers will also examine whether protective antibodies are transferred from the mother to the child. So far, Pfizer has only tested the vaccine in a development study using animals, but the company found no evidence of reproductive problems in these models. The company says it doesn't expect to have data available from the human clinical trial for another six months.

A recent report suggests preliminary study data show **AstraZeneca's** COVID-19 vaccine is effective against the P.1 SARS-CoV-2 strain, a coronavirus variant first detected in Brazil. AstraZeneca has not confirmed this report, nor have efficacy or safety data been released from this study. Last November, a combined interim analysis of data from a phase 2/3 trial in the UK and a phase 3 trial in Brazil found that the company's COVID-19 vaccine AZD1222 was approximately 70 percent effective against infection. Additional analyses found the vaccine had a similar efficacy rate against the UK variant, B.1.1.7, but provided only minimal protection against mild-to-moderate disease from the South African B.1.351 strain. AstraZeneca has previously said it is working to update its vaccine to target new and emerging variants. The company hopes to have the new vaccine version ready by this fall.

Phase 3 trials have launched in Cuba to study the country's COVID-19 vaccine candidate Soberana 2, which was developed by state-run **Finlay Vaccine Institute**. Cuba has already started recruiting for the planned 44,000-person trial in Havana. All trial volunteers must be between 19 and 80 years of age. Participants will receive two doses of the vaccine, and some participants will also receive a third booster vaccine dose with a different Cuban vaccine candidate. Researchers plan to complete the trial in November, and final results should be available in January of next year. Once the results are announced, Cuba plans to also launch late-stage trials of the COVID-19 vaccine in Iran. Cuba says it will vaccinate its entire 11 million population, pending vaccine approval.

VBI Vaccines has initiated enrollment of healthy volunteers in an adaptive phase 1/2 clinical trial studying its enveloped virus-like particle COVID-19 vaccine VBI-2902. Primary endpoints of the trial include safety, tolerability and immunogenicity. In the phase 1 portion, 60 healthy adults between 18 and 54 years of age will receive

continues on next page »

COVID-19 Update

(continued from page 3)

the two-dose regimen. The initial data from this portion of the study is expected by the end of the second quarter. In the phase 2 dose-escalation portion of the study, researchers will evaluate one- and two-dose vaccine regimens. The phase 2 study will be conducted at nine Canadian sites and will stratify people by age (18 to 54, 55 to 65, and 65 and older).

Johnson & Johnson's (J&J) one-shot COVID-19 vaccine has received an interim authorization from Health Canada, which allows the vaccine to be used in the country to prevent COVID-19 in adults. The decision to clear the vaccine was made based on phase 3 trial data. The 43,783-participant trial showed the J&J shot was 85 percent effective for preventing severe COVID-19. Also, the vaccine reduced the risk of hospitalization and death 28 days following inoculation. The J&J vaccine features several advantages over other approved vaccines, such as those from **Moderna** and **Pfizer/BioNTech**, as it can be shipped at common refrigerator temperatures. The vaccine can also be stored for three months in common refrigerator temperatures and up to two years if kept at -4 degrees Fahrenheit. J&J recently announced that it expects to produce up to 10 million doses of its vaccine for Canada by the end of the third quarter.

A new phase 3 study in Brazil suggests **Sinovac's** CoronaVac vaccine may not be effective against the newly identified coronavirus variant from Brazil. The study examined the effectiveness of the vaccine in blood plasma samples from eight vaccinated patients. In the study, the researchers found the Brazilian variant evades protection generated by CoronaVac. The studied plasma samples featured six times less neutralizing capacity against the new strain compared with strains that emerged from the UK and South Africa. Samples from patients who received a booster shot with CoronaVac also showed no signs of neutralization against the Brazilian variant at five months.

Moderna has started to dose trial participants with a modified version of its COVID-19 vaccine in an ongoing phase 2 study to see if the vaccine offers protection against the South African coronavirus variant. The trial is currently on track to enroll 60 participants who have already received a shot of Moderna's COVID-19 vaccine. Participants will receive a booster that has been specifically designed to target the South African variant or a new multivalent vaccine candidate developed by the company to target the original strain and the new variant.

Industry Briefs

Postmarket Trial Failures Lead Some Sponsors to Withdraw Cancer Drugs from the Market

Only about half of oncology drug sponsors granted accelerated approval by the FDA complete postmarket trial requirements the agency sets, and some sponsors have withdrawn products from the market recently in the face of an ongoing FDA review of the accelerated approval program.

In a June 2018 review of all accelerated approvals granted for malignant hematology and oncology indications from the program's inception to May 2017, the FDA found that 40 percent of indications had not finished confirmatory trials or verified clinical benefit at that point. Out of the 93 accelerated approvals, 51 (55 percent) met their postmarket requirement and verified the product's benefit in a median of 3.4 years after the initial approval was given.

Last week, Roche withdrew the bladder cancer indication for Tecentriq (atezolizumab) after its late-stage trial failed to meet its primary endpoint of overall survival in PD-L1-high patients. The company described its withdrawal as being motivated by "an industrywide review of Accelerated Approvals with confirmatory trials that have not met their primary endpoint(s) and have yet to gain regular approvals." The FDA granted Tecentriq Accelerated Approval in 2016.

In another example, at the end of December 2020, Bristol Myers Squibb withdrew its indication for Opdivo (nivolumab) for treating small-cell lung cancer (SCLC) patients whose disease has progressed after platinum-based chemotherapy and at least one other therapy. Opdivo had won accelerated approval for SCLC in 2018 based on its effect on surrogate endpoints from a phase 1/2 trial, but its later confirmatory studies didn't meet primary endpoints of overall survival as required.

Globalization Impacts Racial Disparities in Cancer Clinical Trials

A recent study that looked back at 21 FDA oncology drug approvals from 2015 to 2018 showed that clinical trials conducted primarily outside the U.S. were half as likely to enroll Black participants as trials in the U.S.

Black patients accounted for 3.2 percent of overall enrollment and 5 percent of enrollment in the U.S. Looking at 10,318 patients in those trials, 3,713 participants (36 percent) were enrolled in the U.S. with the remainder from outside the U.S.

The findings were published in the March 8, 2021, issue of the American Cancer Society's peer-reviewed journal, *Cancer*.

Interest in Rare Disease Trials at All-Time High, But Enrollment Problems Persist

Interest in rare disease trial participation is at an all-time high even as the number of trials to treat rare diseases has ballooned, according to two new studies, but enrollment remains difficult.

The National Organization for Rare Disorders (NORD) reports that 88 percent of people living with a rare disease would use an investigational treatment for their condition. At the same time, data from analysis firm GlobalData show the number of rare disease clinical trials increased to almost 5,000 in 2020, up from almost 750 in 2001 — an increase of more than 565 percent.

Despite the growth in trial participation interest and trial activity, more than a quarter of clinical trials targeting rare diseases between 2016 and 2020 had to be terminated early due to low patient enrollment, GlobalData claims.

GlobalData's report cited low enrollment as the most common reason for terminating a trial early, with 26 percent of 736 trials included in the firm's analysis halted for that reason. Other reasons for early termination included lack of efficacy (12 percent), business and strategic decisions (6 percent) and product discontinuation (6 percent).

NORD's study, which compared rare disease trial data from 2019 to those collected 30 years earlier, shows only 62 percent of respondents willing to participate in a trial in 1988. The number of people participating in clinical trials also has increased, with 16 percent of NORD survey respondents reporting they had already participated in a clinical trial, up from 12 percent in 1988.

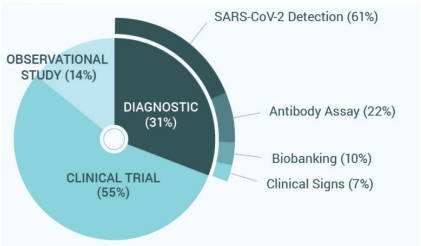
The survey also found that 38 percent of respondents were aware of existing patient registries or natural history studies, which collect longitudinal data to help inform the direction for future clinical R&D of new drugs and therapies. Of the 38 percent of respondents familiar with the registries or studies, 78 percent say they have participated in them. Eighty percent of the respondents said they had not yet participated in either option, but more than half (53 percent) said they would participate if such an option became available for their specific rare disease.

Read the latest NORD report here: https://bit.ly/2PVaXql.

Read the GlobalData analysis here: http://bit.ly/2PQvxlh.

Data Point

Industry-Sponsored COVID-19 Studies Conducted in the U.S., with Diagnostic Study Types



Source: WCG Knowledge Base™

FCRI Update

This Month's FCRI, a Stock Index of 8 Publicly Traded Clinical Trials Companies

Here is this month's First Clinical Research Index (FCRI), a stock index of eight publicly traded clinical research companies. Each month, *CenterWatch Weekly* will publish the calculation of the FCRI, based on the closing stock prices on the last trading day of the prior month, to show how the industry's publicly traded stocks are faring compared to three other widely followed indices: the Standard & Poor's (S&P) 500 index, the S&P Pharmaceutical Index and the S&P Biopharmaceutical Index. For more information about the index, read on.

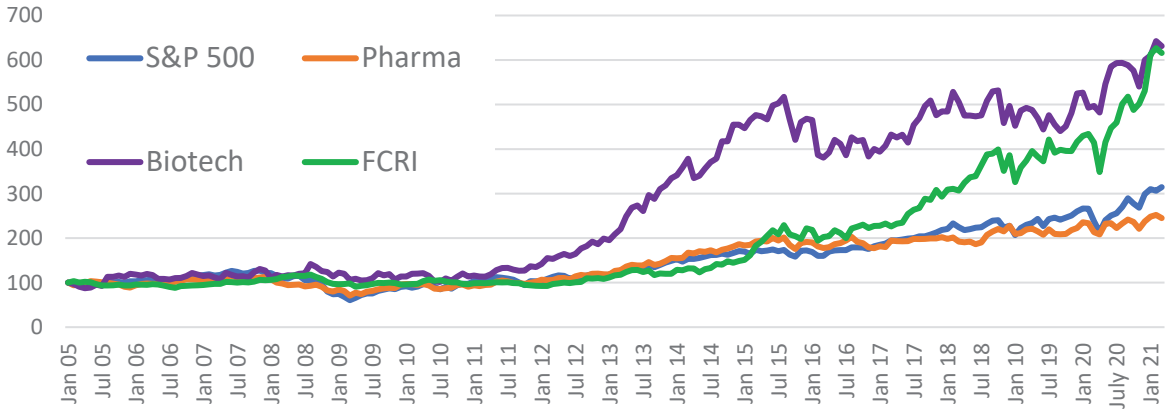
FCRI ▼2%

Biotech ▼2%

Pharma ▼3%

S&P 500 ▲3%

Six FCRI stocks gained and two declined. Significant gainers included Medpace Holdings (+22%), PRA Health Sciences (+20%), EPS Holdings (+11%) and CMIC Holdings (+11%). Significant decliners included Hangzhou Tigermed Consulting (-16%) and ICON (-11%).



NOTES ON INDICES

First Clinical Research Index (FCRI). Calculated as the mean average percentage change from baseline, dividends excluded, adjusted for stock splits. In other words, the indices are not weighted for stock price or market capitalization. Prices are in local currencies. Index components may change from time to time based on new listings, mergers and other factors. Components include eight publicly traded clinical research stocks: CMIC (2309:JP), EPS Co., Ltd. (4282:JP), Hangzhou Tigermed Consulting Co Ltd (300347:CH), ICON (ICLR:US), IQVIA Holdings (IQV:US), Medpace Holdings (MEDP:US), PRA Health Sciences (PRAH:US), and Syneos Health (SYNH:US).
S&P 500 Index (SPX). Capitalization-weighted representative sample of 500 mostly large-capitalization companies in leading industries of the U.S. economy.
S&P 500 Pharmaceutical Index (S5PHARX). Capitalization-weighted S&P 500 companies engaged in research, development or production of pharmaceuticals.
S&P 500 Biotechnology Index (S5BIOTX). Capitalization-weighted S&P 500 companies primarily involved in development, manufacturing or marketing of products based on advanced biotechnology research.

Stock and index prices are available at http://www.bloomberg.com/ and http://bigcharts.marketwatch.com/industry/bigcharts-com/industry chart.asp.

Up and Coming

This feature highlights changes in clinical trial organizations' personnel.

Apollomics

K. Peony Yu has been appointed chief medical officer of Apollomics. Most recently, Yu was chief medical officer at Fibrogen. Apollomics has also appointed **Sophie (Zhengjie) Sun**, a former Merck managing director, to senior vice president of corporate development at the company's China office.

Axcella

Clinical-stage biotech company Axcella has named **Alison Schecter** the president of R&D. Schecter previously served as chief medical officer for Selecta Biosciences.

Axial Therapeutics

A. Stewart Campbell, who most recently served as senior vice president of preclinical R&D at Axial Therapeutics, has been promoted to CEO of the company. Prior to joining Axial in 2017, Campbell was head of business development at CordenPharma.

Biocon Biologics

Susheel Umesh, former CEO of India's Panacea Biotec, has been named chief commercial officer of emerging markets at Biocon Biologics.

Cyclo Therapeutics

Gerald Cox, former chief medical officer of Editas Medicine, has been named acting chief medical officer of Cyclo Therapeutics.

Destiny Pharma

Chief scientific officer of Destiny Pharma, **Bill Love**, has been appointed to the UK Research and Innovation COVID-19 Research and Innovation Taskforce.

Dyne Therapeutics

Wildon Farwell has been named the chief medical officer of Dyne Therapeutics. Most recently, Farwell was vice president and global head of neuromuscular diseases and medical affairs at Biogen.

Ermium Therapeutics

Annegret Van Der Aa has been named chief scientific officer of Ermium Therapeutics. Formerly, Van Der Aa was the chief operating officer at OCTIMET Oncology.

ERS Genomics

Jon Kratochvil has signed on as the vice president for business development and licensing in North America at ERS Genomics. Prior to this new appointment, Kratochvil was director of business development and licensing at MilliporeSigma.

Fulcrum Therapeutics

Bryan Stuart, chief operating officer of Fulcrum Therapeutics, has been promoted to CEO of the company. Before he joined Fulcrum in 2018, Stuart was CEO of Yarra Therapeutics.

Genentech

Lilli Petruzzelli has been named senior vice president of early clinical development at Genentech. Previously, Petruzzelli was group vice president of early clinical development at Incyte.

Gritstone Oncology

Gritstone Oncology's executive vice president of research and chief scientific officer, **Karin Jooss**, has been promoted to head of research and development. **Erin Jones**, Gritstone's executive vice president of global regulatory affairs and quality, was also recently promoted to chief operating officer.

InnoCare

Sean Zhang has departed from his CEO position at Hengrui Therapeutics to assume the role of chief medical officer at InnoCare.

Jubilant Therapeutics

Jubilant Therapeutics has hired **Luca Rastelli** to assume the role of chief scientific officer. Rastelli was most recently the chief scientific officer at Kleo Pharmaceuticals.

Omnicell

Omnicell has named **Christine Mellon** executive vice president and chief people officer. Mellon was most recently chief human resources officer at CSG.

Prometheus Biosciences

Mark Stenhouse has been enlisted to take over the role of chief operating officer at Prometheus Biosciences. Stenhouse most recently served as special adviser to the CEO of Exact Sciences.

Q32 Bio

Jason Campagna, former chief medical officer at Intercept Pharmaceuticals, has been named chief medical officer of Q32 Bio.

Rafael Holdings

Rafael Holdings has recruited **Ameet Mallik** to be its new CEO. Mallik previously was Novartis's executive vice president and head of U.S. oncology

Sagimet Biosciences

Eduardo Bruno Martins is Sagimet Bioscience's new chief medical officer. Martins comes to Sagimet from AbbVie where he was vice president of clinical development.

Shorla Pharma

Nicholas Holsman has been named chief commercial officer of Ireland's Shorla Pharma. Holsman joins Shorla from Oncopeptides, where he served as head of commercial operations.

Solid Biosciences

Solid Biosciences has promoted **Joel Schneider** from chief technology officer to chief operating officer. Schneider was a postdoctoral fellow prior to joining Solid in 2014.

Spaulding Clinical

Neal Collins, former medical director at EMD Serono, has been tapped by Spaulding Clinical as its new medical director.

Features

Increasing Protocol Complexity

(continued from page 1)

The number of trial objectives, endpoints and eligibility criteria has been growing across all three trial phases since 2013, CSDD's data show. From 2013 to 2020, trial objectives increased by 15.9 percent in phase 1, 11.6 percent in phase 2 and 17.6 percent in phase 3. And the number of data points collected in phase 3 trials increased threefold in the past decade (*CenterWatch Weekly*, Jan. 17). Getz says there is little evidence that the growing complexity of clinical trials will abate or recede.

"The timing of CSDD's results is important," Sullivan told *CenterWatch Weekly*. MCC's operating model is to look at work done on specific issues by a variety of different groups and develop practical tools that take the ideas to the next level. "MCC tries to build on the work that other groups have done," she said, "and move it forward."

"Why would we try to redo what CSDD has done?" she asks.

The consortium's Protocol Operational Complexity Scoring Tool, first released in 2017, helps sites evaluate the amount of patient, site and study burden involved in a particular trial's protocol by looking at 20 trial elements, such as use of vendors, patient population and number of site visits. The complexity elements align with TransCelerate's Risk Assessment and Categorization Tool (RACT). RACT is built around a library of more than 100 risk indicators.

"We're going to have to change the way we look at, measure and define many of our metrics moving forward."

—Ken Getz, director of the Tufts Center for the Study of Drug Development (CSDD)

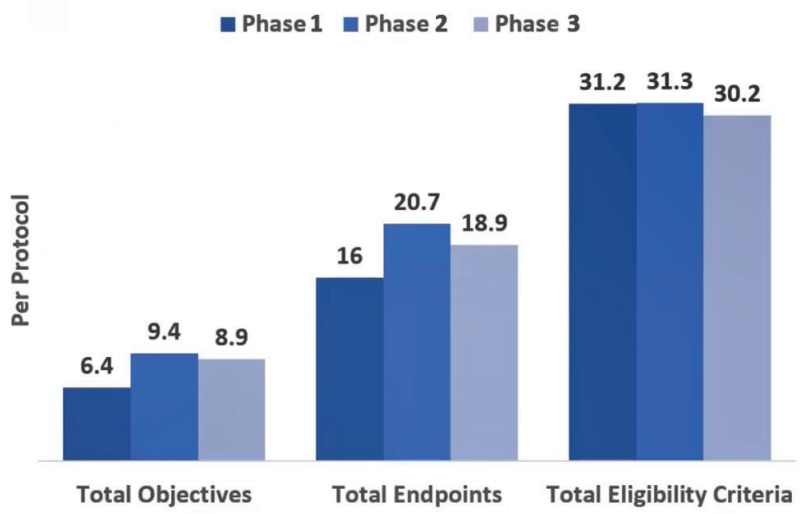
One particularly useful aspect of CSDD's data was the way it broke down trends by therapeutic area, an approach MCC has been considering taking in development of new tools and metrics. For example, CSDD reports that oncology trials have an average of four protocol amendments in phase 2/3 trials, while nononcology trials have an average of 2.7 amendments. "It was exciting for us to see those kinds of breakdowns," she says.

Another aspect of growing protocol complexity that MCC's working group is planning to tackle is its financial impact. More patients, more data points and more deviations all represent additional costs in terms of lengthening studies' timelines, complicating recruitment and retention, and reducing the overall quality of trials, factors the group will consider as it also updates MCC's Cost of Poor Quality Estimator Tool. The tool, which MCC first released in 2017, assesses direct and operational trial costs, extra costs presented by trial extension and the cost of delaying a product's entry into the market.

The MCC working group plans to meet again on May 12 to begin revising the protocol complexity and cost of poor quality tools.

To learn more about MCC's quality improvement working group, click here: https://bit.ly/3eBoWM4.

Increase in Protocol Complexity, 2013 to 2020



Compound Annual Growth Rates (2013 to 2020)			
	Phase 1	Phase 2	Phase 3
Total Objectives	15.9%	11.6%	17.6%
Total Endpoints	1.6%	4.5%	1.6%
Total Eligibility Criteria	3.4%	-0.5%	1.5%

Source: Tufts Center for the Study of Drug Development

Features

Ask the Experts

(continued from page 1)

receipts and reimbursement in cash or check, vouchers for taxis, payment for parking or meals, prefunded debit cards or per-diem payments based on average and expected expenses.

2. **Compensation for Time and Effort** Participants may be compensated for their time and effort, including study visits, tasks outside study visits (completing surveys or diaries) and even travel time to clinical sites. Some ethicists have proposed payment amounts based on local minimum wages, although others have pointed out that compensating at minimum wages may attract only lower-paid persons to participate in research.
3. **Incentive Payments** In some cases, a sponsor may wish to pay a certain amount of money to ensure that they were able to enroll the study with the necessary number of participants and in a reasonable amount of time. An IRB may consider and approve an incentive plan. — Yvonne Higgins, WCG IRB quality assurance adviser

Q: *Many sites offer a referral program for their patients stating, for example, "Refer a friend to our center and receive a $25 gift card." Is this an ethical practice?*

A: The use of referral incentives, sometimes referred to as "snowball sampling," can be an effective recruiting tool, particularly with hard-to-reach populations. The FDA and HHS regulations for human research protections are silent with respect to the payment of incentives in research, whether those incentives are paid to study participants or researchers. However, the regulations do require that the IRB determine that informed consent is sought "only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." (21 CFR 50.20)

The FDA's guidance on payment and reimbursement of research subjects notes that "paying research subjects in exchange for their participation is a common and, in general, acceptable practice," but cautions that IRBs "should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence."

In this case, the role of the person receiving the referral is minimized because they are not directly involved in the study and prospective subjects are being referred to the site, not to a specific study. In other cases, where the referral is for a specific study, there could be a concern that patients would put significant pressure (i.e., undue influence) on their friends or even engage in threatening behaviors (i.e., coercion) to ensure their enrollment in the research so that they would receive the referral incentive.

There are some practical measures that can be put in place to minimize the chance of coercion or undue inducement occurring. The OHRP suggests that "IRBs may restrict levels of financial or nonfinancial incentives for participation and should carefully review the information to be disclosed to potential subjects to ensure that the incentives and how they will be provided are clearly described."

In the case of referral fees, IRBs may consider the structure of proposed referral plans and suggest limitations to referral plans that minimize the potential for coercion of undue inducement. Limitations might include restricting the number of referrals an individual may make or not having the referral payment be contingent on the enrollment of the referred individuals. Many IRBs do not allow payment of referral fees to medical professionals or research staff.

Finally, the consent process should minimize the chance of coercion or undue inducement occurring. Referred individuals should understand that the choice to participate is voluntary, and the role of the individual making the referral should be minimized. — David Borasky, vice president of IRB compliance

Q: *Will an IRB allow reimbursement for co-pays for routine patient care costs associated with participation in a clinical trial when the costs are covered by insurance but the subject is responsible for a high co-pay? Examples of these costs include extra blood tests, scans or administration of medication other than the study drug.*

A: The IRB can approve this but there may be other parties that have to weigh in. While it is not ethically objectionable to reimburse out-of-pocket expenses for research participation, there may be potential legal issues with reimbursement of co-pays. It is illegal to pay for co-pays under Medicare, and many private insurers have elected to follow suit. As a result, having a research sponsor reimburse co-pays could lead to legal issues for the research physician and the insured individual. — David Borasky, vice president of IRB compliance

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status	Sponsor Contact
COVID-19 Trials and Actions				
Kintor Pharmaceutical	proxalutamide	male COVID-19 outpatients	IND approved by the FDA for phase 3 trial	en.kintor.com.cn
Melior Pharmaceuticals	tolimidone	nonhospitalized patients recently diagnosed with COVID-19	IND approved by the FDA for phase 2 trial	meliorpharmaceuticals.com
AIM ImmunoTech	intranasal Ampligen	prophylaxis or early-stage treatment for COVID-19 and other respiratory viral diseases	first patient dosed in phase 1 trial	aimimmuno.com
VBI Vaccines	VBI-2902	COVID-19 vaccine	first patients enrolled in phase 1/2 trial	vbivaccines.com
Can-Fite Biopharma	piclidenoson	patients hospitalized with moderate- to-severe COVID-19	first patient enrolled in phase 2 trial	can-fite.com
Other Trials and Actions				
Alphamab Oncology	KN046	thymic carcinoma	IND approved by the FDA	alphamabonc.com
TissueTech	TTAX03	facet joint pain resulting from osteoarthritis	IND approved by the FDA	tissuetech.com
Lee's Pharma	socazolimab	extensive-stage small-cell lung cancer	IND cleared by China's National Medical Products Administration for a phase 3 trial	leespharm.com
Alteogen	Eylea Biosimilar (ALT-L9)	neovascular (wet) age-related macular degeneration	completion of phase 1 trial	alteogen.com
BioEclipse Therapeutics	CRX100	refractory solid tumors	first patient dosed in phase 1 trial	bioeclipse.com
American CryoStem	autologous mesenchymal stem cell infusion therapy	postconcussion syndrome	phase 1 trial initiated	americancryostem.com
Impact Therapeutics	Wee1 Inhibitor IMP7068	patients with advanced solid tumors	first patient dosed in phase 1 trial	en.impacttherapeutics.com
Adicet Bio	ADI-001 allogeneic gamma delta T-cell therapy expressing a chimeric antigen receptor	B-cell nonHodgkin lymphoma	phase 1 trial initiated	adicetbio.com
BeiGene	BGB-15025 hematopoietic progenitor kinase 1 (HPK1) inhibitor	T-cell activated cancer growth	phase 1 trial initiated	beigene.com
Oncoinvent	Radspherin	ovarian cancer patients with peritoneal carcinomatosis	first patients enrolled in third-level dose cohort of phase 1 trial	oncoinvent.com
DemeRx	ibogaine HCl (DMX-1002)	opioid use disorder	phase 1/2a trial authorized in the UK	demerx.com
Aravive	AVB-500	patients with advanced clear-cell renal cell carcinoma that have progressed on front-line treatment	first patients dosed in phase 1b/2 trial	aravive.com
Metacrine	MET642	nonalcoholic steatohepatitis	first patient treated in phase 2a trial	metacrine.com

continues on next page »

Drug & Device Pipeline News (continued from page 11)

Company	Drug/Device	Medical Condition	Status	Sponsor Contact
OCON Health	intrauterine drug delivery platform IUB SEAD	abnormal uterine bleeding	patient enrollment complete in phase 2a trial	oconmed.com
AEON Biopharma	BP-450 (prabotulinumtoxinA) injection	preventive treatment of migraine	initiation of phase 2 trial	aeonbiopharma.com
Edesa Biotech	EB01	chronic allergic contact dermatitis	patient enrollment complete in first cohort of phase 2b trial	edesabiotech.com
IRLAB Therapeutics	mesdopetam	levodopa-induced dyskinesias in Parkinson's disease	first patients dosed in Europe in phase 2b/3 trial	irlab.se
Natera	Signatera tumor-informed, personalized molecular residual disease test	muscle-invasive urothelial carcinoma	phase 3 trial initiated to test use of diagnostic tool prior to treatment with Genentech's atezolizumab (Tecentriq)	natera.com
Caladrius Biosciences	CLBS12	Buerger's disease	Orphan Drug designation granted by the FDA	caladrius.com
Sigilon Therapeutics	SIG-007	Fabry disease	Orphan Drug designation granted by the FDA	sigilon.com
Steba Biotech	Padeliporfin ImPACT	adults with upper-tract urothelial cancer	Orphan Drug designation granted by the FDA	stebabiotech.com
Passage Bio	PBGM01	GM1 gangliosidosis	Fast-Track designation granted by the FDA	passagebio.com
Passage Bio	PBFT02	frontotemporal dementia with granulin mutations	Fast-Track designation granted by the FDA	passagebio.com
Passage Bio	PBKR03	Krabbe disease	Fast-Track designation granted by the FDA	passagebio.com
Rocket Pharmaceuticals	RP-L201	leukocyte adhesion deficiency-I (LAD-I)	Regenerative Medicine Advanced Therapy designation granted by the FDA	rocketpharma.com
Genentech	Actemra (tocilizumab) subcutaneous injection	systemic sclerosis-associated interstitial lung disease	approved by the FDA	gene.com
Kite Pharma	Yescarta (axicabtagene ciloleucel)	relapsed or refractory follicular lymphoma after two or more lines of systemic therapy	approved by the FDA for expanded indication	kitepharma.com
Seqirus	Flucelvax	quadrivalent influenza vaccine	approved by the FDA for expanded age indication	seqirus.com
Roche	Ventana ALK (D5F3) CDx Assay	companion diagnostic to identify ALK-positive nonsmall-cell lung cancer patients eligible for treatment with Pfizer's Lorbrena (lorlatinib)	approved by the FDA	roche.com
Able Medical Devices	Valkyrie Thoracic Fixation System	stabilization and fixation of fractures of the chest wall	approved by the FDA	ablemedicaldevices.com
Brain Scientific	next-generation NeuroCap device	electroencephalogram electrode array used to obtain rapid EEGs in routine clinical and research settings	approved by the FDA	brainscientific.com

JobWatch

The Source for Clinical Research Jobs and Career Resources

Twice monthly, *CWWeekly* provides featured listings of clinical research job openings, upcoming industry conferences and educational programs from **JobWatch**, CenterWatch's online recruitment website for both clinical research employers and professionals.

Jobs via Kelly Services

Clinical Lab Scientist
Baton Rouge, LA

Laboratory Supervisor
West Bloomfield, MI

Senior Clinical Data Manager
Seattle, WA

Research Associate
San Diego, CA

Clinical Research Scientist
Raynham, MA

Analytical Chemist
Detroit, MI

Clinical Laboratory Scientist
Ferndale, MI

Entry-Level Chemist
Cincinnati, OH

Scientist II, Formulation Development
Seattle, WA

Quality Control R&D Lab Tech
Norcross, GA

[VIEW ALL KELLY SERVICES JOBS]

More Jobs

Coordinator, Clinical Research
Southeast Georgia Health System
Brunswick, GA

Clinical Data Manager
WCG MedAvante-ProPhase
Hamilton, NJ

Project Manager - Clinical Research
WCG MedAvante-ProPhase
Tokyo, Japan

Associate Project Manager - Clinical Research
WCG MedAvante-ProPhase
New York, NY

Project Manager - Patient Enrollment
WCG ThreeWire
Eden Prairie, MN

Logistics Coordinator
WCG MedAvante-ProPhase
Hamilton, NJ

Project Manager
WCG Trifecta Clinical
Indianapolis, IN

Project Manager - Clinical Research
WCG MedAvante-ProPhase
New York, NY

[VIEW ALL JOB LISTINGS]

Upcoming Event Highlights

Virtual Conferences

MARCH 23 & MARCH 25, 2021

Data Integrity for GCP Professionals: *Core Requirements, Expectations and Challenges*
10:00 a.m. – 4:30 p.m. EDT

This interactive virtual workshop will give you the tools you need to ensure your clinical trials' electronic records are trustworthy and reliable across their entire data lifecycle, from initial data creation through long-term archives.

APRIL 26-29, 2021 & MAY 3-6, 2021

MAGI's Clinical Research vConference
11:00 a.m. – 5:00 p.m. EDT

A meeting that matters… more than ever. MAGI sessions and workshops emphasize practical tips based on real-life examples, with lots of interaction.

SEPT. 28 – SEPT. 30, 2021

Clinical Trial Risk & Performance Management vSummit
9:00 a.m. – 4:00 p.m. EDT

Through this summit, you'll have the opportunity to delve into the ways metrics can help you navigate your clinical trials with thoughtful effort and unprecedented success.

[VIEW ALL EVENTS]

wcg CenterWatch
www.centerwatch.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431
Phone: 866.219.3440 or 617.948.5100
Customer Service: customerservice@centerwatch.com

Editorial Director: Beth Belton, 703.538.7641, bbelton@wcgclinical.com
Reporter: Charlie Passut, 703.538.7664, cpassut@wcgclinical.com
Sales: Russ Titsch, 813.767.6463, russ.titsch@centerwatch.com