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The Citeline Awards, now in their fifth year, recognize the people and organizations that drive drug development forward. This year, as with so much of 2020, the Citeline Awards event was significantly disrupted by the arrival of the novel coronavirus. Just as nominations for the awards were closing in February 2020, so began a cascade of shutdowns across the globe. Amidst the chaos of the pandemic, it is only fitting to carry on the awards that salute the clinical R&D professionals who dedicate their lives to developing new medicines that treat, cure and prevent human disease.

The Digital Citeline Awards provided an opportunity to celebrate the successes of 2019, safely. Thanks to the power of technology, the event enabled professionals from across the globe to participate, network and applaud one another's work. This year's award presentations concluded with a special tribute to "COVID Heroes" -- those working tirelessly to find treatments and vaccines to help end the pandemic. For anyone who may have missed the event, you can watch on demand to see the highlights (https://next.brella.io/join/Citeline20).

The extraordinary events of 2020 have pushed industry to take bold and innovative steps in order to advance clinical research under very difficult circumstances. Transformative initiatives in trial design, clinical operations, regulatory science, and cell and gene therapies are highlighted in the enclosed articles prepared by Scrip, Pink Sheet and In Vivo. I invite you to read on and share these insightful pieces with your colleagues.

Congratulations to the 2020 Citeline Awards winners and thank you to everyone who entered and shared their inspiring stories of determination and success. I extend my sincere appreciation for the generosity of our sponsors, and for the generous donation of time and discriminating insights provided by our panel of judges, without whom this event would not be possible.

The entire world is counting on clinical research professionals like you to pull us out of this pandemic; based on the achievements showcased at the 2020 Citeline Awards, I can confidently say "you got this."

Karen Currie
Executive Director, Citeline Editorial
Pharma Intelligence

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THE 2020 DIGITAL CITELINE AWARDS WINNERS

CONGRATULATIONS TO THE AWARD WINNERS

The Digital Citeline Awards took place on 17th September 2020.

Talaris Therapeutics
CLINICAL TRIAL RESULT OF THE YEAR

Acorn AI by Medidata (a Dassault Systèmes company)
BEST USE OF ARTIFICIAL INTELLIGENCE IN CLINICAL TRIALS

Biohaven Pharmaceuticals, Clinical Operations Team
CLINICAL RESEARCH TEAM OF THE YEAR

TCS Connected Clinical Trials, Janssen Pharmaceuticals
BEST PATIENT-FACING TECHNOLOGY INITIATIVE

Acorn AI by Medidata (a Dassault Systèmes Company) – Synthetic Control Database™ (SCD)
BEST SPONSOR-FACING TECHNOLOGY INITIATIVE

GBT
EXCELLENCE IN RARE DISEASE DRUG DEVELOPMENT, SPONSORED BY BIOHAVEN PHARMACEUTICALS

Medicsensors
MOST SUCCESSFUL EARLY PHASE RESEARCH (PRECLINICAL & PHASE I)

Adapttech
MOST INNOVATIVE START-UP COMPANY

Janssen, CISCRP, MedEvoke & Peer Plus
MEDIDATA CLINICAL PARTNERSHIP OF THE YEAR, SPONSORED BY MEDIDATA

Novartis
MARQUEE AWARD R&D EXCELLENCE

COVID-19 Pandemic Accelerates Shift Toward Virtual Trials

MELANIE SENIOR

In providing tests and medicines to blunt COVID-19's devastating effects, the pharma sector has a once-in-a-generation chance to prove its value to all of society

As the global shut-down caused by the coronavirus pandemic continues, sponsors are rushing to adapt clinical trials that can move to partial or completely remote monitoring, allowing patients to remain in their homes but continue to participate in studies. And the outbreak may have another silver lining for the biopharma industry, a chance to rebuild its reputation.

- Virtual trials have long been technically feasible, but cultural barriers have slowed their uptake.
- The COVID-19 pandemic has changed that, compelling sponsors to go remote where possible and underlining the advantages of at-home data collection and digitally mediated support.
- Supportive regulators may catalyze wider acceptance of these new ways of working, increasing the likelihood that changes will endure post-coronavirus. New mind-sets may also boost other attempts to drive R&D efficiency – and lower prices

If virtual clinical trials had not quite taken off before coronavirus hit the world, they certainly are now. "It feels like every sponsor is coming to us and asking how much of their existing trials can be virtualized, or at least go partly remote," said Greg Licholai, chief medical officer at PRA Health Sciences, a contract research organization. There is now a dramatic, urgent shift to embrace models that have been technically feasible for many months, even years, but which cultural and mind-set barriers have hitherto blocked. "The majority of trials will adjust to include more remote monitoring and potentially more remote data collection," said Licholai.

The pandemic has shut down population movements and transport systems across large parts of the world, preventing many clinical trial patients from attending

trial sites – and restricting principal investigators (PIs) and other clinical staff to their homes. Hence the flurry of trial delays and cancellations: Bristol-Myers Squibb Co., Pfizer Inc., Merck & Co. Inc. and Eli Lilly & Co. are among the growing list of companies to have announced a stop to new trial starts, and pauses to recruitment into existing studies, for the next several weeks. A survey of US clinical trial sites carried out by consultancy Continuum Clinical on 12-13 March found that one third expected a significant impact on trial recruitment and execution – and that was before the strictest restrictions came into force in many areas. Polls carried out since then report even higher levels of actual and expected disruption.

As the shut-down continues, sponsors are rushing to adapt those studies that can move to partial or completely remote monitoring, allowing patients to remain in their homes but continue to participate in a trial. IQVIA's CEO reassured clients in a 24 March letter that it was transitioning "significant portions of trials to virtual platforms to enable study continuity," elaborating that services and technologies were being deployed to further increase remote-based clinical research associates, to enable remote interactions between patients and health care providers where possible, and centralized trial monitoring. Jonathan Cotliar, chief medical officer at California-based Science 37 Inc., which specializes in virtual trials, reports growing interest in the company's services as sponsors adjust trial protocols in order to minimize in-person patient interactions. "Some sponsors have suspended recruitment in all their trials except for the virtual studies they are running with us," said Cotliar.

Alongside the ethical and commercial incentives to keep trials running, there is support from regulators, too. US and UK authorities are signalling a willingness to allow for appropriate modifications to trial protocols, urging sponsors to document whatever data-gaps or changes do arise because of the virus to minimize the impact on trial integrity.

Encouraged by regulators' openness to protocol modifications, Adial Pharmaceuticals announced that it was modifying a pivotal Phase III trial of its alcohol use disorder drug AD04 to include tele-medicine-based assessments and behavioral treatment, with fewer, shorter, in-person visits. A full-scale shift to remote monitoring would be too complicated for many studies, however, requiring massive protocol amendments and jeopardizing data integrity as a result. But "most will adapt and incorporate what can be done easily," noted PRA Health Sciences' Licholai.

J&J Goes Virtual: Heartline And CHIEF-HF

And some will not have to adapt at all. Johnson & Johnson has launched two fully virtual trials since the start of 2020. The first, Heartline, uses the Apple Watch plus a specially designed app to screen patients for atrial fibrillation, irregular heart rhythms that can signal an increased risk of stroke. The CHIEF-HF trial is a drug intervention study, investigating whether SGLT-2 inhibitor Invokana (canagliflozin) can help improve quality of life among heart failure patients.

Invokana has been approved since 2013 as a diabetes drug; it was the first in its class to reach the market. But it has since been overtaken by AstraZeneca PLC's Farxiga (dapagliflozin) and Lilly/Boehringer Ingelheim International GmbH's Jardiance (empagliflozin), not least because it was linked in 2016 to a greater risk of lower limb amputation. This study, carried out in collaboration with PRA Health Sciences, is Janssen's bid to leap-frog its competitors into gaining a wider label among patients with heart failure symptoms (whether diabetic or not), using an approach that is much cheaper and faster than conventional trials. CHIEF-HF was originally designed as a conventional trial. But that was found to be far too expensive – even with just 300 patients – given the competitive landscape.

The virtual version was launched during the week commencing 16 March, just as the world shut down. Despite that, 44 patients were screened during that first week at a single delivery system, after responding to emailed invitations (electronic medical records were used to check patient eligibility), and five other systems are yet to activate. "Under the old approach, recruitment would have been zero," said John Whang, head of cardiovascular and metabolism integrated evidence at Janssen. CHIEF-HF will recruit close to 2,000 patients, cost about a tenth of a traditional study, and may take only half the time – even in the current landscape. "It has been eye-opening that

Regulators Show Support

In guidance published 18 March, the FDA showed it was willing to be flexible in accepting certain adjustments to clinical trial practices, so long as patient safety was maintained. For instance, it suggested that some investigational drugs may be amenable to "alternative secure delivery methods" to patients, helping reduce trial-site visits. It urged sponsors to evaluate whether "alternative methods for safety assessments (e.g. virtual visit, phone contact) could be implemented" to assure participant safety.

The UK Medicines and Healthcare products Regulatory Agency (MHRA), in guidance issued 19 March, is similarly being "as flexible and pragmatic as possible with regard to regulatory requirements for clinical trials during this time." It supports remote monitoring (phone calls instead of an in-person study visit) where possible, without requiring substantial amendments to update trial protocol. It simply asks sponsors to document any changes internally.

The FDA is allowing any urgent changes required in order to limit patient exposure to COVID-19 to be reported after (rather than before) they are made. But modifications to how efficacy endpoints are collected, including a switch to virtual assessments or data collection, should be run past the appropriate FDA review division.

These are broad-brush guidelines for now; detail is lacking. As the disruption continues, sponsors will need more specific information on the nature and scope of acceptable and unacceptable changes.

we are still able to function in this environment," Whang continued. He reported a willingness to keep going, despite everything; even recruitment centers carrying out data analysis to determine eligibility said it was important to "continue to do what they could to keep things on track."

Similarly, in Heartline, "we're still seeing 30 [new recruits] each day," said Whang. It is a slow-down from the 5,000 pulled in over the five days following the 25 February launch – the virus outbreak drowned out the marketing effort for this direct-to-patient screening study. But it is something.

The CHIEF-HF study will track patients' physical activity (steps, stairs climbed) and sleep using a wearable device and collect patient-reported outcomes via app-based questionnaires. The objective is to determine whether the drug – which is drop-shipped to participants' homes – can improve quality of life compared to placebo in individuals with preserved or reduced ejection fraction heart failure, and with or without diabetes. J&J is hoping this trial will expand the drug's label to include patients with symptomatic heart failure, but no diabetes.

AstraZeneca and Lilly/Boehringer are going after the same goal, using multi-thousand patient randomized controlled Phase III outcomes studies. AstraZeneca's DAPA-HF and DELIVER trials involve almost 5,000 and over 6,000 patients, respectively. (DELIVER is due to report in 2021; DAPA reported topline data last September and the drug is under priority FDA review.) Both of Lilly's EMPEROR trials are due to report later this year. If all goes to plan – a big if, given current circumstances – Farxiga could get a heartf failure indication for both diabetes and non-diabetic patients during the first half of 2020, with Jardiance a year or so later. With CHIEF-HF, Johnson & Johnson is trying to change the order of entry.

It might not work. CHIEF-HF is not an outcomes study; it is a real-world (pragmatic) trial, albeit a randomized controlled one. The treatment period is just three months, with six further months' observation. It is unclear whether the physician community will assume that positive outcomes data translates across the SGLT-2 class, as J&J hopes. Nor is it clear whether they will perceive eventual symptom-improvement data from CHIEF-HF as trumping further positive outcomes data from AstraZeneca and Lilly/Boehringer, if it emerges.

Yet regulators are increasingly open to patient-reported symptoms and to real-world evidence more broadly. Given continued unmet need in heart failure, the FDA in June 2019 issued draft guidance on endpoints for heart failure drugs stating that "an effect on symptoms or physical function, without a favorable effect on survival or hospitalization risk" can be a basis for approval. (The guidance emerged to correct many sponsors' belief that favourable mortality and morbidity endpoints were required.)

The Growing Value Of Virtual

Whether or not CHIEF-HF can reverse Invokana's fortunes, the trial will have provided J&J and PRA Health Sciences with experience in how to set up and run a virtual trial – experience that looks likely to become increasingly valuable post-coronavirus. "Irrespective of how the trial works out, we both walk away with know how" around how to run lots of different studies in future, enabling significant efficiency improvements across many trials, says Whang.

Heartline was an important virtual training ground. With no active drug intervention and with the consumer appeal of the Apple Watch, this was the low hanging fruit. It provided some of the expertise required for J&J to move to CHIEF-HF – like app design, remote randomization processes and claims data. (Janssen co-developed with Apple an app to connect the irregular rhythm detector on the back of the watch with the electrocardiogram device, prompting patients to take an ECG measurement when they get an arrhythmia notification.) More importantly, the Heartline study helped bring more minds on board. It "opened the door for the [internal] conversations around making CHIEF happen," said Whang, who was instrumental in driving both studies.

The whole CHIEF enterprise took years to get off the ground. Besides working out the nitty gritty around study design, accurate data collection, connectivity, usability and traceability, there was some resistance internally and from the investigator physician and clinician community. One example: asking patients to consent and to confirm they had taken their medication via a digital channel, as opposed to face-to-face. "The accepted way is that you must face the patient," said Whang. But, short of watching a patient swallow the drug (which can also be done via camera), many investigators still rely, during in-person visits, on a patient's word that they have taken the medication. So, the shift to virtual communication – as COVID-19 forces care delivery to adopt telemedicine at an unprecedented pace – is less stark than it might seem.

Cost and convenience arguments were already, pre-coronavirus, slowly driving some corners of the industry toward decentralized trials. Virtual or hybrid trials are underway across areas of dermatology, rheumatology behavioural health and in some neurological disorders like multiple sclerosis (for instance, using wearable movement-tracking devices). The pandemic is likely to accelerate that, as people are forced to embrace digital tools faster and more comprehensively than they would have ever imagined – and as their advantages become clearer still. "The current situation may transform how the industry thinks about clinical trial execution and the inherent benefits for a more patient-centric, virtual model," said Science 37's Cotliar. William Stilley, CEO of addiction-focused Adial Pharmaceuticals, said that the company's adjustments to its Phase III trial may increase retention rates, due to the less onerous visiting schedules, boost the study's statistical power, and reduce its cost.

Post-coronavirus, some restrictions may remain in place, and individuals – particularly those with underlying conditions – will remain wary of crowded spaces and unnecessary hospital visits. Any secondary outbreaks would further sharpen such concerns. In that context, hybrid trials – involving some in-person elements alongside remote tracking – will likely "become the new normal," predicted Licholai. Such trials can be used across a wide range of medicines, including self-injected biologics, for instance. They will not mean an end to in-person office visits, just fewer of them. "There is a lot that can be done, such as patients going to independent local sites for blood draws, or for CAT scans," said Licholai. Clinicians and regulators, like individual patients, are likely to be much more receptive to such methods.

Even now, mid-crisis, Licholai was optimistic. Speaking on 23 March, he said he had not yet seen a dramatic slow-down in progression of new clinical research – though PRA's focus on oncology, many forms of which are life-threatening, may mean they are less impacted than some other CROs. Earlier-stage projects were rapidly pivoting to become virtual or hybrid, he said.

While scientists in hubs such as Boston use skeleton staff to maintain essential experiments, others are shifting to locations with less stringent restrictions, such as Ukraine or indeed China. "China's contract research organizations are almost back up to full speed," claimed Alexis Borisy, veteran biotech entrepreneur, venture capitalist, and chair and CEO of EQRx.

If coronavirus does catalyze faster, cheaper and

shorter trials for some products and new indications, that should, in theory, enable lower drug prices.

Fertile Ground For A New R&D Model

Lower drug prices is EQRx's mission. To achieve it, the company will make use remote trial technology. But that is just part of a plan to comprehensively re-engineer how drugs are developed and distributed. As was widely reported in January 2020 when the company came out of stealth mode with $200m in funding, EQRx aims to create equally good, or better, drugs than those currently available – and to sell them at "a radically lower price" than existing options, said Borisy.

The start-up is not a charity, though. It hopes to be just as profitable as traditional firms, thanks to being much more efficient – and free of the legacy costs and infrastructure that encumber traditional pharma firms. The "EQ" in the company's name stands for emotional quotient – a company which "understands what people and society want and need," said Borisy.

After this pandemic – the duration of which is unknown, despite President Trump's most optimistic guesses – society is going to be very clear on what it wants and needs. Access to cheap medicines will be top of the list for many, alongside freedom to see friends and family and to escape the confines of their home. The economic shut-down will have pushed many millions into financial difficulty, risking negative health consequences that stretch well beyond those caused directly by the virus.

EQRx will not be selling 10 new medicines by Christmas. But it does aim to launch 10 drugs over 10 years, starting in inflammatory diseases and oncology, the epicentres of high-priced drugs. Borisy would not say what targets the company was going after first – only that they are known biological targets. That means there is little scientific risk. But the company will take advantage of the best of what is available – including in designing small molecules and engineering antibodies, as well as in creating newer modalities like nucleic acid-based technologies. In development, too, it will use all the digital and virtual tools in the box.

Technology And Trust

Particularly at the commercial end, EQRx will deploy a non-technological tool that has the potential to radically accelerate patient access to new drugs: trust. Its lower-price mission means EQRx starts out with payers and providers on its side – in contrast to most of the rest of the sector. (Outspoken price critic Peter Bach, oncologist and director of the center for health policy and outcomes at Memorial Sloan Kettering Cancer Center, is an EQRx co-founder and advisor.) That trust will open the door for EQRx to work directly with payers and providers, and with independent health technology assessment bodies, in determining the optimal kinds of evidence required to prove cost-effectiveness. Those stakeholders will likely help gather that evidence, too. "There is a lot of room to think about how you are doing studies, in addition to your core regulatory grade trials," said Borisy.

EQRx will not be a panacea for drug pricing and access. It will have to establish its own costs and infrastructure as it scales up – and, even with its ambitious timelines, it will need years to get more than a handful of drugs to market. It will face IP-related lawsuits from those selling the valuable drugs that its programs threaten.

But, rather as studies like Heartline and CHIEF-HF may do for Johnson & Johnson and the wider R&D community, EQRx will show there is another way. Its impact on drug prices may ripple out well beyond its own potential treatments – analogous to when low-cost airlines pulled down prices among traditional carriers (in what now seems like a bygone era).

This viral pandemic has not spared any country, health system or economic sector. Its impact on everyday lives, communities and economies is likely to lead many individuals and industries to radically re-think how they operate and what they prioritize.

That backdrop will provide fertile ground for efforts like EQRx, and for virtual trials like CHIEF-HF and Heartline. And the outbreak may have another silver lining for the biopharma industry. In providing the tests, medicines and perhaps one day the vaccines required to blunt the virus' devastating effects, the sector has a perhaps once-in-a-generation chance to prove its value to all of society, and to re-build a reputation that has languished at the bottom of the league.

Rare Disease Gene Therapy Guidance Gives More Flexibility On Placebo-Controlled Trials

SUE SUTTER

The US Food and Drug Administration declined stakeholder requests to eliminate a recommendation for placebo controls in a final guidance document on rare disease gene therapies but provided more flexibility around their use "when feasible."

In the final guidance, Human Gene Therapy for Rare Diseases, the agency bowed to industry concerns about the 2018 draft guidance and removed language on biomarker validation.

However, the FDA reinforced its call for early establishment of critical quality attributes and critical manufacturing process parameters – a recommendation that appears aimed at balancing the potential use of Phase I data to support approval with the need to have a well-characterized product and manufacturing process before beginning that Phase I study.

The rare disease guidance was released in late January along with five other gene therapy final guidances, including recommendations on chemistry, manufacturing and controls information and hemophilia product development. (*Also see "US FDA Expects Updates On Investigational Gene Therapy CMC Improvements" - Pink Sheet, 28 Jan, 2020.*) (*Also see "Gene Therapies: US FDA Sticks With Bleeding Rate For Hemophilia Approval Endpoint" - Pink Sheet, 9 Feb, 2020.*)

The agency also issued a draft guidance on gene therapy sameness determinations under the orphan drug regulations. (*Also see "Orphan Exclusivity For Gene Therapies Hinges On Two Big Factors" - Pink Sheet, 28 Jan, 2020.*)

Sticking With Placebo Controls ... When Feasible

Like the draft guidance, the final guidance acknowledges the challenges of conducting studies in small patient populations and provides for use of historical controls and alternative study designs.

Nevertheless, the final document reiterates a preference for randomized, controlled trials, with inclusion of a placebo arm where appropriate.

In the draft guidance's discussion on early-phase studies, the agency said clinical programs should include evaluation of two or more dose levels to help identify one or more potentially therapeutic doses. "Ideally, placebo controls should be added to each dose cohort," the draft guidance said.

The emphasis on randomized trials and mention of placebo controls in the draft document raised concerns among some stakeholders.

"Placebo controls, when feasible, are recommended to facilitate the interpretability of both safety and efficacy results. If a study has multiple dose-level cohorts, consider randomizing some subjects in each cohort to receive placebo." – FDA

While in most cases a randomized, concurrent-controlled trial is the preferred study design, "the challenges inherent in rare disease patient recruitment require alternative clinical trial designs," the Biotechnology Innovation Organization's comments state.

BIO requested removing the recommendation for placebo controls in each dose cohort "because it conflicts with recommendations elsewhere in the guidance where the agency indicates flexibility on alternative trial designs, which may not encompass placebo controls."

"The mention of placebo controls in each dose cohort is not consistent with the greater flexibility and discussion around appropriate controls in other parts of the guidance," Pfizer Inc.'s comments state. "We recommend that the mention of placebo controls be removed or that a conditional statement be added such as, 'Ideally, placebo controls should be added to each dose cohort when other appropriate controls cannot be identified as discussed in this guidance.'"

Similarly, the American Society of Gene and Cell Therapy's comments urge the FDA to qualify "the recommendation for placebo-controlled dose-finding studies for settings in which it is feasible."

The agency declined requests to remove the discussion of placebo controls from the final guidance but did add some qualifying language.

"Placebo controls, when feasible, are recommended to facilitate the interpretability of both safety and efficacy results," the final guidance states. "If a study has multiple dose-level cohorts, consider randomizing some subjects in each cohort to receive placebo."

The final guidance's discussion on study designs also reflects new language on concomitant medications.

"In some situations, study subjects may continue to take their pre-study medication(s), particularly if medication discontinuation would pose substantial risks, and if use of such concomitant medication(s) would not interfere with the objectives of the trial," the guidance states. "The dose of concomitant medication should be stable over a specific time period (e.g., until measurement of the primary endpoint), which should be justified in the clinical protocol."

Biomarker Validation Language Removed

In the final guidance, language on biomarker development was moved from the section on dose selection to study designs and revised in the process.

In the draft guidance, the FDA said efforts should be made early in development to "identify and validate biomarkers and to leverage all available information from published investigations for the disease of interest (or related diseases)."

The language around biomarker validation was called out in stakeholder comments.

"Validation of biomarkers is a significant challenge and requiring validation would likely be prohibitive for most rare diseases," Pfizer said. "The recommendation to validate should be removed or additional clarification should be added regarding the opportunity to establish a correlation that is 'reasonably likely to predict a clinical benefit,' which could be used for accelerated approval."

"Validation of biomarkers at an early stage may present significant challenges for rare diseases," comments from bluebird bio Inc. state. "We recommend that FDA provide additional guidance on how to validate biomarkers for rare and ultra-rare diseases."

Sponsors should characterize a gene therapy's critical quality attributes for product concentration, potency, identity and purity, and implement manufacturing critical process parameters, before initiating clinical studies.

The agency heard the concerns around biomarker validation. The final guidance was revised to remove the instruction to validate biomarkers early in development, instead stating that efforts should be made to "identify relevant biomarkers and to leverage all scientifically relevant information from published investigations for

the disease of interest (or related diseases)," with the added qualifier "to the extent possible."

In the case of biomarkers or endpoints that are closely linked to the underlying pathophysiology of the disease, such as a missing metabolite in a critical biosynthetic pathway, "changes in such biomarkers could be used during drug development for dose-selection, or even as an early demonstration of drug activity."

New Language on Accelerated Approval

The final guidance's language on efficacy endpoints also explains the type of evidence needed to support use of a surrogate endpoint for accelerated approval.

The sponsor should provide sufficient data to support a conclusion the proposed endpoint is reasonably likely to predict clinical benefit, the final guidance says. "In general, such data should, at a minimum, demonstrate a correlation between changes in the proposed surrogate endpoint and a beneficial clinical effect."

CMC Work That Should Be Completed Before Phase I

The guidance also includes more specificity on CMC recommendations, particularly with regard to product quality work that should be done before clinical trials begin.

Sponsors should characterize a gene therapy's critical quality attributes (CQAs) for product concentration, potency, identity and purity, and implement manufacturing critical process parameters (CPPs), before initiating clinical studies, the final guidance states. The draft guidance had stated that product CQAs should be characterized and manufacturing CPPs should be implemented "during early clinical development."

"Innovative strategies for understanding CQAs may include applying prior knowledge from other similar products, leveraging product characterization data from nonclinical studies, evaluating CPPs during engineering runs, or the production of multiple small lots versus a single large product lot," the final guidance states.

The FDA tightened its recommendation on the early timing of characterization of product CQAs and CPPs despite stakeholder objections to the draft language.

BIO said characterization of manufacturing CPPs during early clinical development is not appropriate considering the likely additional changes to the manufacturing process. "The recommendation for manufacturing CPPs should be on a case-by-case basis depending on the stage of development and maturity of the manufacturing process."

Pfizer said that although accelerated development will be aided by earlier CMC work, "flexibility will still be needed to allow manufacturing process improvements throughout development. For example, experience in manufacturing product for clinical trials is essential in developing CQAs and therefore only potential CQAs would be available before first in human studies."

The final guidance also notes that when changes to the manufacturing process are necessary, a comparability assessment may be needed.

In addition, the document addresses the development of potency assays to assess functional activity, consistency and stability, and to provide evidence of comparability after manufacturing process changes.

"To better understand product function(s), we strongly encourage the evaluation of multiple product characteristics before initiating clinical studies," the guidance states. "These characterization studies may in turn be used to establish a potency test, which is critical to successful product development."

"Therefore, we recommend that a potency test that measures a relevant biological activity be qualified for suitability (i.e., accuracy, precision, sensitivity, specificity) prior to conducting trials intended to provide substantial evidence of effectiveness for a marketing application and validated prior to licensure," the guidance states.

FINALIST

EXCELLENCE IN RARE DISEASE DRUG DEVELOPMENT

Alexion Pharmaceuticals

Donnan, living with aHUS

We are honored to be twice-named a finalist in the Excellence in Rare Disease Drug Development category for our advancements in the treatment of atypical hemolytic uremic syndrome (aHUS) and neuromyelitis optica spectrum disorder (NMOSD).

For 25 years, Alexion has been a leader in rare disease with a foundation in complement biology, allowing us to innovate in areas where there is great unmet need and opportunity to help patients and families. With this focus, we developed the first-and-only approved complement inhibitor for NMOSD and redefined the standard of care for people living with aHUS. These advancements would not have been possible without the patients who participated in the clinical trials, the caregivers who supported them, the trial investigators, and the dedicated employees at Alexion.

With a mission to transform the lives of people affected by rare diseases, Alexion thanks all the finalists in this category for their dedication to improving the lives of patients and families.

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How To Use Digital Technology For EU Drug Approvals

IAN SCHOFIELD

The European Medicines Agency has produced new guidance for pharmaceutical companies wanting advice on the use of digital technology-based tools in drug development and the preparation of marketing authorization applications (MAAs).

Digital technologies are increasingly being used in clinical trials, for example in monitoring patients' clinically relevant parameters, digital remote monitoring of drug intake, and electronic patient signatures on informed consent forms.

Technologies that might be used include sensors (ingestibles and implantables), mobile health tools such as wearables for remote patient monitoring, video consultations with patients, health data analytics and digital record systems.

If such technologies are to be used to support product evaluation, approval and post-approval monitoring, and if they are expected to have an impact on the benefit-risk assessment, it is important to ascertain whether they are "in line with, better, or less reliable" than more established methods of data capture, says the guidance, which is in the form of a Q&A.

Companies wanting to seek advice on the use of digital technologies can use the EMA's qualification (validation) or scientific advice procedures during product development, according to the agency. It says "early contacts" are encouraged to help applicants identify the best way of getting such advice "and to advise on the content of submissions."

The following are examples of digital health technologies that would fall within the scope of the qualification program: digital endpoints, digital biomarkers, electronic clinical outcome assessments (eCOAs) and digital measures.

Early Dialogue Needed

Applicants can request qualification advice at any time during the development of the digital technology, but "the importance of early dialogue is emphasized," the guidance says. As there is much to learn about digital technologies, an iterative qualification process is "a possible and often desirable option for applicants."

A submission for qualification "should provide insight into the reliability, accuracy, precision, clinical validity, generalisability and clinical applicability of the methodology to be qualified," the guidance says. The submission should focus on how the technology will provide clinically meaningful data "and not on requirements how to meet technical specifications."

In the qualification process the EMA will look at "whether the clinical measure taken with the technology is fit for the intended use in regulatory decision making during drug development, whether a clinically meaningful interpretation of the concept of

interest is possible, and whether or not the underlying method used is reliable and robust."

The agency also points out that qualification is not required if the digital technology is used in an exploratory way in early trials – for example in proof of concept studies before pivotal development. The need for qualification "arises once the technology is used to support or collect the main body of data that will be considered pivotal to the assessment of the benefit-risk balance of a new medicine."

Not all aspects of a digital technology will necessarily fall within the EMA's remit, and there may be "a degree of overlap between the remits of authorities responsible for different parts of the assessment," for example a medicinal product versus a medical device.

"From the experience so far, when submitting to EMA it is useful to frame the questions and supportive documentation in the context of medicinal product development and subsequent benefit-risk evaluation, as this increases the likelihood of the question being accepted and of the response being relevant," the agency remarks.

The EMA also notes that while it has no experience of trials that are exclusively conducted remotely or with digital tools, the situation is "rapidly evolving." The use of digital technologies to supplement in-clinic visits "could support progressive increase of knowledge and trust in digital technologies, if transparency and a strong dialogue and collaboration between scientists, developers of technology, companies and the regulatory network is maintained," it declares.

A draft guideline on electronic systems and data in clinical trials is under development by the agency's Good Clinical Practice Inspectors Working Group, which focuses on digital data entry and will consider aspects such as audit trails, system validations and electronic informed consent, it notes.

Take-Home Messages

In conclusion, the EMA offers five "take-home" messages that companies should bear in mind when preparing a submission for qualification:

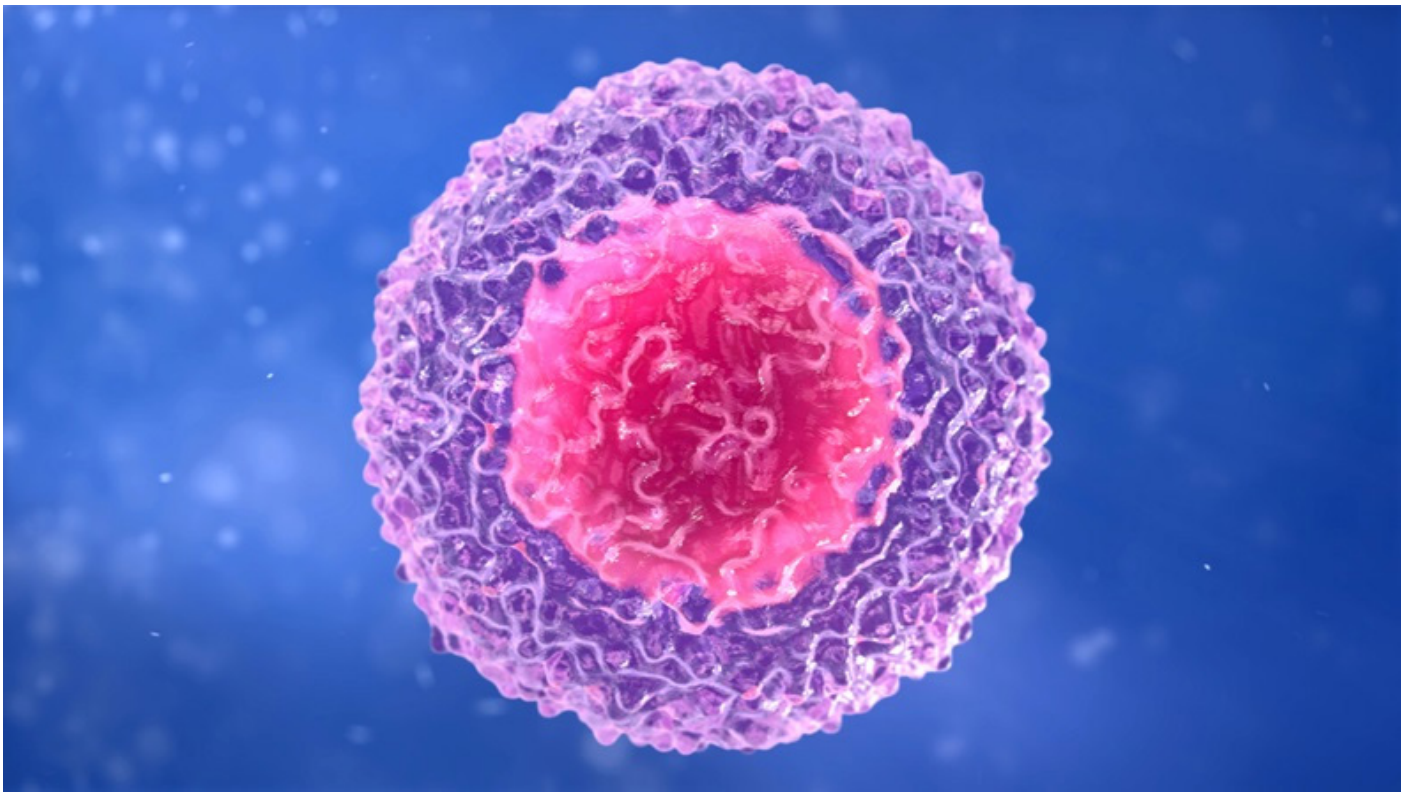
- Start interacting early. This allows the relevant experts to be identified and should result in shorter review times by allowing the EMA to provide input on the content, timing and format of the request.
- Identify a clear research question. Issues such as the concept involved and details of how it will be used "should form the backbone of the thinking process behind a qualification submission." It should also be made clear whether the technology is an alternative to an existing method or is "intended to measure something intrinsically different."
- Be focused and specific. Vague or open questions are likely to receive general answers; the document makes suggestions on how to present the information in a systematic manner.
- Frame the questions in a manner relevant to the stakeholders. Because of the possible overlap between different remits, wording a question from the perspective and remit of a given decision-maker "increases the likelihood of the question being accepted, appropriately addressed, and the assessment being relevant."
- Provide a draft best practice. The applicant should provide a guidance for implementation of the technology in clinical trials or explain the key points of the methodology that will be used.

Data Protection

The agency adds that applicants must note the "utmost importance" of ensuring compliance with EU data protection requirements "in light of the sensitive health data processed by the device to be used in combination with the proposed medicinal product." It is not within the EMA's remit to assess such compliance, it adds.

Encouraging Signals For New Cancer Cell Therapy Strategies

MANDY JACKSON



Chimeric antigen receptor T-cell therapies have shown remarkable efficacy in leukemia and lymphoma patients who relapsed or were refractory to several prior treatments, but many challenges remain in the cancer cell therapy field. Strategies that may improve upon first-generation therapies were presented during the American Association for Cancer Research virtual meeting with encouraging early activity, but these treatments also have hurdles to overcome.

Data from the first patients treated with novel cell therapy constructs and combinations from Gracell Biotechnologies Co. Ltd., Iovance Biotherapeutics Inc., Gilead Sciences Inc. and the US National Cancer Institute were presented on 28 April during AACR's plenary session on adoptive cell transfer therapy. The AACR meeting was changed from a 24-29 April convention in San Diego to an online event scheduled for 27-28 April and 22-24 June due to the COVID-19 pandemic.

These next-generation approaches attempt to address issues such as CAR-T cell persistence, loss of response due to antigen escape, the lack of T-cell therapies for solid tumors and the weeks-long manufacturing required for autologous products. (*Also see "Next-Generation CAR-Ts Tackle First-Generation Safety, Solid Tumor Challenges" - Scrip, 21 Apr, 2018.*)

Gracell's Allogeneic CAR-T Has Novel Target

The first two CAR-T therapies approved globally – Gilead subsidiary Kite Pharma Inc.'s Yescarta

(axicabtagene ciloleucel) and Novartis AG's Kymriah (tisagenlecleucel) – are autologous therapies requiring extraction of patients' own T-cells, which the companies reengineer to target CD19 before the cells are expanded and infused back into patients.

Allogeneic products, like Gracell's GC027, use healthy donor cells so that CAR-T therapies can be manufactured as off-the-shelf medicines for on-demand treatment. GC027 is being tested in relapsed or refractory (R/R) T-cell acute lymphoblastic leukemia (T-ALL), which affects about 20%-25% of adult ALL patients and 12%-15% of pediatric ALL patients. The standard of care for T-ALL is multi-agent chemotherapy and most patients progress within two years.

Kymriah is approved in the US to treat pediatric and young adult patients with R/R B-cell ALL and adults with R/R large B-cell lymphoma; Yescarta also is approved for R/R large B-cell lymphoma. Both products take about two weeks to manufacture after T-cells are withdrawn from patients, which is enough time for blood cancers to progress so much that patients are no longer good candidates for CAR-T therapy.

GC027 targets CD7, an antigen present in about 95% of T-ALL. Gracell engineered the allogeneic CAR-T therapy with its TruUCAR technology platform, knocking out the donor cells' T-cell receptor (TCR) to prevent graft-versus-host disease (GvHD) associated with the donor cells; CD7 also was knocked out of the engineered T-cells so the CAR-T cells wouldn't attack each other – a process known as fratricide. (*Also see "Regulatory Blessings Helping China CAR-Ts March Closer To Global Cancer Patients?" - Pink Sheet, 12 Dec, 2019.*)

Suzhou- and Shanghai-based Gracell's Xinxin Wang presented the findings from five T-ALL patients treated with three different doses of GC027 – one-time infusions of 8 million, 10 million or 15 million cells. All patients achieved complete remission with or without complete blood count recovery (CR/CRi), including four (80%) who were minimal residual disease (MRD)-negative. Two patients have since relapsed, however.

Wang noted that there doesn't seem to be a relationship between tumor burden and CAR-T cell expansion with GC027. But in terms of cell expansion and efficacy, she said a patient who responded at day 14 and relapsed at day 29 had the least CAR-T cell expansion of the five patients in the study.

The GC027 cells took about 10-14 days to expand in the treated patients and persisted for about three weeks, which Wang said was enough time to eliminate T-ALL cells and put patients into remission. Longer persistence could lead to infections, she added.

No GvHD or neurotoxicity was observed, but all GC027-treated patients experienced cytokine release syndrome (CRS). Neurotoxicity and CRS are common side effects with CAR-T therapies and can be severe, even deadly. Four patients treated with GC027 had grade 3 CRS and one had grade 4 CRS.

Wang noted that the aggressive lymphodepleting chemotherapy regimen given to patients before treatment with GC027 to make room for the reengineered T-cells may have contributed to the high rate and severity of CRS events.

Yvonne Chen from the David Geffen School of Medicine at the University of California, Los Angeles (UCLA), as the discussant for the GC027 data presentation, said the high doses Gracell tested also may have contributed to high CRS rates. However, she also said the absence of GvHD and neurotoxicity with GC027 was impressive.

Chen noted that highly engineered CAR-T cell technology platforms require a delicate balancing act. As more genetic alterations are made to knock out certain elements to improve persistence and function, she said there could be more impacts to CAR-T cell stability and uniformity.

Iovance's TILs Show Efficacy In Advanced Lung Cancer

Iovance has shown that its autologous tumor-infiltrating lymphocyte (TIL) technology is able to effectively treat advanced relapsed and refractory solid tumors with impressive response rates in early clinical testing for melanoma and cervical cancer. The company anticipates filing its lead TIL candidate lifileucel with the US Food and Drug Administration

for approval to treat melanoma in 2020, making it the most advanced T-cell therapy technology in the clinic.

TILs are extracted from patients' tumors, expanded ex vivo and then reengineered to evade the tumor's immuno-suppressive environment and boost TIL replication and activation. Like CAR-T therapies, the TIL therapy is delivered back to the patient in a one-time infusion. The technology's efficacy in solid tumors spurred talk of a potential Iovance acquisition earlier this year. (*Also see "Iovance TIL Appeal Seen Luring Potential Buyers" - Scrip, 26 Feb, 2020.*)

Data from a Phase I clinical trial in non-small cell lung cancer, which was conducted by investigators at H. Lee Moffitt Cancer Center in Tampa, FL for TIL candidate LN-145, were presented at AACR by Moffit's Ben Creelan. This study, which was supported by Iovance and a Stand Up To Cancer Catalyst Grant, justified initiation of two NSCLC cohorts in the company's basket trial known as IOV-COM-202. LN-145 is being tested in the Phase II Iovance-sponsored study as a monotherapy and in combination with Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab).

Metastatic NSCLC patients in Moffit's Phase I study received four doses of the Bristol-Myers Squibb anti-PD-1 antibody Opdivo (nivolumab) and stayed on therapy if they responded. If not, they received lymphodepleting chemotherapy (cyclophosphamide and fludarabine) before treatment with LN-145 and an interleukin-2 (IL-2); the IL-2 promotes TIL expansion.

Two out of 13 evaluable patients achieved durable complete responses (CRs), both lasting for longer than a year. Four patients have confirmed or unconfirmed partial responses (PRs), if the fourth PR is confirmed, the overall response rate will be 33%.

The most common adverse events were cytopenias related to lymphodepleting chemotherapy; Creelan said there was almost no on-target, off-tumor toxicity.

Gal Markel of Sheba Medical Center in Israel, the discussant for Creelan's presentation, noted several unanswered questions, including whether or not the four doses of Opdivo administered before LN-145 contributed to patients' responses and how this treatment regimen would work in older, sicker individuals – patients with cardiovascular co-morbidities were excluded from the study.

However, Jefferies analyst Biren Amin said in a 27 April note based on the AACR abstract for Creelan's presentation that a 10% CR rate would have been clinically meaningful, so the 15% CR rate seen in the study was impressive. Amin pointed out that the CR rate for Opdivo alone is 4% in second-line metastatic NSCLC and 1% in the third-line setting.

PD-1 Didn't Improve Yescarta Efficacy, But Studies Continue

Data for Kite's CD19-targeting CAR-T therapy Yescarta in combination with Roche's PD-L1 inhibitor Tecentriq (atezolizumab) in the treatment of refractory diffuse large B-cell lymphoma (DLBCL) did not show an improvement in Yescarta's efficacy. Caron Jacobson from Dana-Farber Cancer Institute in Boston presented the results, which came from the Phase I/II open-label study ZUMA-6.

The AACR presentation covered data from 28 patients, most of whom were enrolled in the Phase II portion of the study. Some of the patients were enrolled in Cohort 3 of the Phase I portion of the study, which determined the Yescarta/Tecentriq dosing for Phase II.

Immune checkpoints, including PD-1 and PD-L1 have been shown to be upregulated in tumors and after CAR-T cell infusion, the ZUMA-6 investigators hypothesized that PD-L1 inhibition would augment Yescarta activity.

However, the overall response rate in Kite's ZUMA-1 study, which supported approval of Yescarta monotherapy, was 83% and the CR rate was 58%. But in the ZUMA-6, the ORR was 75% and the CR rate was 46% in the 28 patients receiving combination therapy, showing that Tecentriq did not improve Yescarta's efficacy. Tecentriq did not improve expansion of CAR-T cells in ZUMA-6, Jacobson reported.

In terms of safety, 27 patients in the ZUMA-6 data experienced CRS. All but one of the CRS events were Grade 1 or 2; the other was Grade 3. There were 19 neurological events, including eight Grade 3 or 4 events, but no Grade 5 events. The safety profile in this study was similar to prior Yescarta trials.

Jacobson said further analysis of ZUMA-6 will consider whether certain patient groups are more likely to benefit from combination PD-L1/CAR-T therapy, but more studies are needed to better understand the interaction of CAR-T cells and PD-1/PD-L1 inhibition.

Discussant Markel noted that preclinical studies justified testing this combination in patients and said the results overall were encouraging in terms of justifying additional testing in patients.

A Gilead spokesman told *Scrip* that "we are performing further analysis of ZUMA-6 data to better understand whether there are identifiable patient populations who may derive benefit from this combination approach, and this will inform our decision on how best to proceed."

NCI Continues To Evaluate Bispecific CAR-T

Haneen Shalabi, from the National Cancer Institute Pediatric Oncology Branch, reported results from the first 13 patients treated with an NCI-developed autologous CAR-T cell construct targeting both CD19 and CD22 for the treatment of children and young adults with relapsed or refractory B-cell ALL.

This bispecific therapy was designed to overcome the challenge of antigen escape, which happens in ALL when patients who respond to CD19-targeting CAR-T therapy but have a relapse when there are no more CD19-expressing cancer cells for the CAR-T cells to attack. By targeting CD19 and CD22, the NCI researchers hypothesized that their bispecific treatment would continue to eliminate leukemia cells because the CAR-T cells were engineered to seek out two different antigens.

Six patients (46%) had CRS and two (15.4%) had Grade 3 or higher CRS, while one patient (7.7%) experienced Grade 3 neurotoxicity. All of these adverse events were reversible.

Five out of 12 evaluable patients experienced complete remission – all of those patients were treated at the middle of three doses tested and all five responders were MRD-negative. Two patients relapsed with CD19/CD22-positive ALL at 265 days and 123 days after infusion with the bispecific CAR-T cells. The other three responders remain in remission at one to eight months post infusion (median of seven months).

While the CD19/CD22 CAR-T cells showed clinical activity with limited and reversible neurotoxicity, Shalabi noted that there was a discrepancy between responses observed in bone marrow and in extramedullary (EM) disease, which suggests limited delivery of CAR-T cells to EM sites. The NCI investigators determined that higher doses may be needed to address this issue, but close monitoring and longer-term follow-up are needed to understand the bispecific cells' impact on EM disease.

The ongoing study may incorporate a higher dose and patients may be separated by disease burden, since patients with higher disease burden had better responses. Also, the lymphodepleting chemotherapy used prior to CD19/CD22 CAR-T administration is being intensified for patients who previously received CAR-T therapy to overcome immune-mediated resistance. A new manufacturing process, evaluation of CAR-T products to understand T-cell exhaustion, and co-administration of a checkpoint inhibitor to boost efficacy in EM disease also are being considered.

Discussant Chen from UCLA said CD22 is a confirmed target for the treatment of B-cell ALL, but patients treated in studies of CD22-targeting CAR-T therapies have been more likely to stop responding to treatment due to antigen escape. The CD19 functioning was dominant in the bispecific CD19/CD22 CAR-T cells tested by NCI, she noted.

However, Chen also pointed out that T-cell exhaustion or functional issues appear to have been the problem in this study rather than antigen escape, so the NCI needs to assess its manufacturing process to improve bispecific CAR-T cell persistence and function going forward.

WINNER

CLINICAL RESEARCH TEAM OF THE YEAR

Biohaven Pharmaceuticals

Biohaven is a clinical-stage biopharmaceutical company with proven leadership in industry and academic settings. Our portfolio is comprised of innovative, late-stage product candidates targeting neurological and neuropsychiatric diseases, including rare disorders. Our progress is fueled by an entrepreneurial organizational structure and an impressive range of experience in drug development along with the confident support of top-tier biopharma investors.

Biohaven has combined internal development and research with intellectual property licensed from companies and institutions including Bristol-Myers Squibb Company, AstraZeneca AB, Yale University, Catalent, ALS Biopharma LLC and Massachusetts General Hospital.

Since our initial public offering in 2017, we have made rapid progress with multiple compounds across our CGRP receptor antagonist, glutamate modulator, and myeloperoxidase (MPO) inhibitor platforms. Nurtec™ ODT (Rimegepant 75 mg) received FDA approval in February 2020 and is quickly gaining traction as the only orally disintegrating CGRP antagonist for acute treatment of migraine. At the same time, Biohaven is advancing novel acute and preventive treatments for migraine with zavegepant and rimegepant. In addition to continued exploration of our CGRP receptor antagonists, multiple clinical trials are ongoing for product candidates across our neuroinnovative platforms.

biohaven™ pharmaceuticals

biohaven pharmaceuticals

Biohaven is a biopharmaceutical company focused on the development and commercialization of innovative best-in-class therapies to improve the lives of patients with debilitating neurological and neuropsychiatric diseases.

Neuroinnovation

Biohaven's Neuroinnovation portfolio includes Nurtec™ ODT (rimegepant) for the acute treatment of migraine in adults and a broad pipeline of late-stage product candidates across three distinct mechanistic platforms – calcitonin gene-related peptide (CGRP) receptor antagonism, glutamate modulation and myeloperoxidase (MPO) inhibition.

> "Our three Neuroinnovation platforms are focused on evaluating the next generation of treatments for a diverse set of diseases in large markets and orphan indications in which there are currently limited or no treatments available."
>
> – Vlad Coric, M.D., CEO of Biohaven

CGRP Platform: Migraine

Treatment with a CGRP receptor antagonist is believed to relieve migraine by reversibly blocking CGRP receptors, thereby inhibiting the biologic activity of the CGRP neuropeptide.

Nurtec ODT is the first and only FDA-approved CGRP receptor antagonist in an orally disintegrating tablet (ODT) for the acute treatment of migraine in adults.

Nurtec ODT achieves positive results in pivotal trial for the preventive treatment of migraine, meets primary endpoint in reduction of monthly migraine days.

Biohaven is also developing zavegepant for the acute and preventive teatment of migraine. Zavegepant is the first CGRP receptor antagonist drug candidate designed to be administered in an intranasal formulation.

Glutamate Platform: Neurologic and Neuropsychiatric Disorders

Abnormal glutamate release is known to disrupt nerve health, potentially leading to neuronal cell death which is associated with devastating neurodegenerative diseases.

Biohaven is developing the next generation of agents aimed at normalizing glutamate via two distinct mechanisms: glutamate-transporter modulation or N-methyl-D-aspartate (NMDA) receptor antagonism.

- Troriluzole is in development for the treatment of Alzheimer's disease, obsessive-compulsive disorder and spinocerebellar ataxia.
- BHV-5000 is an orally-available, first-in-class, low-trapping, NMDA receptor antagonist for initial indications in rare CNS diseases, pain and depression.

MPO Platform: Neuroinflammation

Myeloperoxidase (MPO) is one of the most important enzymes for generating oxidative stress and inflammation. Inhibition of MPO activity may reduce production of oxidants that feed neuroinflammatory processes, thereby slowing progression of several neurodegenerative diseases.

Biohaven's first candidate from the MPO platform is verdiperstat, a potent, first-in-class, brain-penetrant MPO inhibitor for the treatment of multiple system atrophy and amyotrophic lateral sclerosis.

- Initiated Phase 3 trial in multiple system atrophy
- Initiated platform trial at Massachusetts General Hospital, Healey Center for amyotrophic lateral sclerosis

AT A GLANCE

Founded: September 2013

Employees: 300

Headquarters: New Haven, CT

Executive Management

Vlad Coric, M.D.
Chief Executive Officer and Director

James Engelhart, C.P.A.
Chief Financial Officer

Cliff Bechtold, M.S.
Chief Operating Officer

Elyse Stock, M.D.
Chief Medical Officer

Charles Conway, Ph.D.
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US FDA, Industry Share Early Lessons From Complex Innovative Trial Designs Program

SUE SUTTER

Sponsor readiness, a well-thought-out trial design, and giving the US Food and Drug Administration all the data it needs to thoroughly vet a complex innovative study proposal are keys to a successful experience under the agency's pilot program.

For the FDA's part, it is working to ensure that staff involvement with a particular trial design does not end after the second of two meetings allowed under the pilot program.

Industry participants and officials from the FDA's drug and biologic product centers shared their early experiences with the complex innovative trial design (CID) meeting pilot at the Drug Information Association's recent annual meeting.

"In just a couple years we've had about a dozen sponsors come in with proposals to the program and each of those proposals has represented a real creative effort on the part of the sponsors, a courageous effort to creatively address their drug development problems," said John Scott, director of the Division of Biostatistics in the Center for Biologics Evaluation and Research.

"Not every one of those proposals has ultimately been considered well suited for the pilot program, but they were all thoughtful and they were all the product of serious thinking about scientific issues underlying the specific case," Scott said.

The CID pilot has received 11 submissions, with five accepted.

The CID pilot fulfills a commitment under the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI). It is intended to provide drug developers with an opportunity to discuss CID approaches – such as complex adaptive, Bayesian and other novel trial designs – with the Center for Drug Evaluation and Research or CBER. The pilot program is jointly administered by CDER's Office of Biostatistics and CBER's Office of Biostatistics and Epidemiology. (*Also see "Complex Innovative Designs Pilot Likely Satisfies Industry's Disclosure Worries" - Pink Sheet, 29 Aug, 2018.*)

The agency will accept up to two designs submitted by sponsors per quarter. Industry participants have the opportunity for two meetings with FDA staff within a span of approximately 120 days to discuss trial design details. Participation carries certain public disclosure requirements so the FDA can use the trial designs to show what kinds of approaches are acceptable. (*Also see "US FDA Offers Sponsors More Attention For Sharing Complex Innovative Trial Designs" - Pink Sheet, 3 Apr, 2018.*)

To date, there have been 11 submissions to the pilot program, 10 for CDER and one for CBER, the FDA told the *Pink Sheet*. Of the 11 submissions, five were accepted into the pilot meetings program, all in CDER. CBER did not accept the one submission it received, the agency said.

Need A 'Fully Baked' Trial Design

Two of the early CID pilot participants were from Wave Life Sciences Ltd. and Eli Lilly & Co. (*Also*

see "Neurology At The Forefront Of US FDA Complex Innovative Trial Design Pilot" - Pink Sheet, 1 Apr, 2020.) Representatives from both companies talked about the experience at the DIA meeting.

Wave was accepted into the program for a Phase II/III trial for suvodirsen for treatment of Duchenne muscular dystrophy patients amenable to exon 51 skipping.

Stephen Lake, VP of biometrics, said Wave had two primary objectives in designing the DYSTANCE 51 trial: maximize the probability of a definitive result on a clinical endpoint, the North Star Ambulatory Assessment, which would be needed for drug approval in the EU and Japan; and be able to identify a treatment effect on dystrophin levels through an interim analysis prior to study conclusion, which potentially would have allowed for accelerated approval in the US.

To maximize the probability of a definitive NSAA result, Wave wanted to incorporate the capability to augment the placebo arm with historical data. This required gaining access to historical control data sets, and the company focused primarily on placebo arm data from past clinical trials of DMD candidates.

While Wave was formulating its study design, the FDA announced the CID program. The company submitted an application in September 2018 and in November 2018 was notified of its acceptance into the program's first round.

The company's first meeting with the agency under the CID program was in late January 2019. However, the second meeting was delayed to June 2019 to provide time for simulations to be conducted after the first meeting, Lake said.

Under the CID timeline, the briefing document for the second meeting would have been due two weeks after the first meeting, a deadline "which we could not meet," Lake said. In addition to extending the deadline, the agency granted the company another two teleconferences during the pilot to discuss details and progress.

Lake pointed to several challenges in the trial's design. In particular, gaining access to historical data can be difficult given the number of parties and complicated process involved.

With the help of the Critical Path Institute, Wave secured access to Lilly's tadalafil and PTC Therapeutics Inc.'s ataluren pivotal trial placebo data. While the company was in discussions with Pfizer Inc. to access the domagrozumab clinical trial placebo data, the big pharma conducted analyses on those datasets to assist with Wave's clinical trial simulations.

In total, Wave had data from approximately 271 placebo patients from other trials, a number that was reduced to about 190 eligible controls when the DYSTANCE 51 key inclusion criteria were applied, Lake said.

"When you are applying for the program and certainly prior to that first meeting, you really have to have almost everything completed, and it should then be sort of fine-tuning after the first meeting in anticipation of the second meeting."
– Wave Life Sciences' Stephen Lake

However, clinical endpoint instruments and training had evolved over time, which complicated the use of the historical data, Lake said.

In addition, innovative trial designs necessitate extensive up-front documentation, including the data monitoring committee charter, independent statistical center charter, statistical analysis plan and data access plan, he said.

Unfortunately for Wave, an analysis of a Phase I open-label extension study showed no impact of suvodirsen treatment on dystrophin levels, and the company decided to discontinue development of the compound.

"So while it's very disappointing to not see this trial through to completion, I still think it's important to talk about the study design and our participation in CID to inform others who are in rare disease drug development," Lake said.

He described the CID program as providing a productive sounding board for innovative trial design.

"There were well-attended meetings with statistical group support from across different offices and

divisions of the FDA," he said. "We got insights from reviewers with experience in different therapeutic areas, and FDA demonstrated flexibility in response to our emerging needs in terms of delaying the second meeting as well as granting us two additional telecons."

The CID program timelines are tight, especially if a sponsor is also engaging with other regulatory agencies, Lake said.

Sponsors that are considering applying for the program should do so only if they have "a fully baked trial design," he said.

"When you are applying for the program and certainly prior to that first meeting, you really have to have almost everything completed, and it should then be sort of fine-tuning after the first meeting in anticipation of the second meeting," Lake said. "We were somewhat unable to do that because we were still trying to access historical datasets almost throughout the process of the CID program, so we had a number of different competing timelines all going on at once."

Lilly's Pain Master Protocol

Lilly was accepted into the CID pilot for development of a master protocol that enables multiple drugs to be studied in multiple types of chronic pain through use of disease state addenda and intervention-specific appendices.

The master protocol allows for direct comparisons of assets within and between pain types, as well as standardized data collection on efficacy, safety and biomarker data, JonDavid Sparks, principal research scientist at Lilly, said.

Key features of the master protocol include common scales for assessing: pain using a numeric rating scale (with data collected daily on an electronic device); physical functioning; emotional functioning; and patient global assessment.

In addition to the same primary endpoint across the master protocol, other standardized elements include: randomization of 33% of patients to placebo in each substudy; an eight-week double-blind period; common visit schedules and data collection methods; and identical inclusion/exclusion criteria. At the intervention-specific level, additional scales, visits and inclusion/exclusion criteria can be added, and sample sizes can be specified.

One of the biggest benefits of the master protocol is it allows the sample size of both the active and placebo arms to be reduced by borrowing placebo information within a pain type and treatment effect information between pain types, Sparks said.

One of the biggest challenges to proceeding under the CID pilot is whether the timing of engagement with the FDA fits well within a particular development program, Sparks said.

Like Wave's Lake, Sparks noted the window between the first meeting under the pilot and the deadline for the second briefing document is quite short, although the agency was flexible with the timeframe.

Continuity Of Interactions A Concern

Sparks also raised concerns about continuity of agency interactions and advice on the master protocol after completion of the two meetings under the pilot.

While the pain master protocol may continue to live for many more years, it may be difficult to continue the dialogue with the same group of FDA staffers who first commented on the protocol design, Sparks said. "That would be something that is a bit of a challenge and is something that would be nice to continue there," he said.

"We have been trying to work to make sure that there is some continuity over time … so as you come in, once you're done with those two meetings you're not done with the CID program."
– FDA's Laura Lee Johnson

Lake also raised similar concerns about being able to engage with specific agency staff on a particular trial

design once the CID pilot activities are completed.

After Wave's second meeting with the agency, "we felt like we had this great dialogue and really were hoping to continue the engagement with the people who had participated in the CID program," Lake said. However, the company subsequently discontinued the drug's development, so there was no opportunity to say, "This is where we're at. Can we talk with some of the CID people again?"

Laura Lee Johnson, division director in CDER's Office of Biostatistics, said the agency is working to address concerns about continuity of interactions over complex innovative trial designs.

"We have been trying to work to make sure that there is some continuity over time … so as you come in, once you're done with those two meetings you're not done with the CID program," Johnson said. "We are trying to help with that as staffing allows."

Challenges For The FDA, Too

Like industry, the FDA also has seen some challenges with the early experience with the CID pilot.

One of these is that the agency needs more information early on, particularly around simulation plans and results, than it is being given by sponsors, Johnson said.

She said the FDA has outlined the types of information it wants to see from CID participants in an August 2018 *Federal Register* notice and in two guidances – a September 2019 draft guidance on interacting with the FDA on complex innovative trial designs, and a November 2019 final guidance on adaptive designs.

"You don't take this very lightly," Johnson said. "It takes a lot of work to actually move through this, but the type of work that FDA is asking for is also what many sponsors will need to do in order to move forward and make decisions about their programs. But without that information we can't make a decision either."

"Many times we don't have as detailed of a simulation plan as we need. We don't have a detailed simulation report that's submitted, or some of the parameters aren't varying that we thought would be varying, or the range doesn't match the historic information," Johnson said. "So really providing more robust information to the FDA has been something that I think for us definitely speeds up our review."

Johnson said sponsors need to consider whether they are ready to submit a request to participate in the CID program, and whether this is the optimal time to meet with FDA.

CID Learnings Reverberate Outside Pilot Program

Johnson also highlighted the importance of the program's public disclosure component, citing as an example Wave's decision to discontinue suvodirsen's development.

Because the trial was stopped, under typical circumstances the agency would not have been able to discuss the design, she said.

At CBER, "what we have had is at least a couple dozen truly complex innovative proposals come in just under regular IND during this time, and I think part of that is this sort of increased era of openness and open discussion that the pilot program has helped promote." – FDA's John Scott

"We would have had all of that back and forth but we wouldn't be able to talk about it publicly," Johnson said. "Because they were in that CID program, FDA can publicly disclose certain aspects of the design because of the disclosure agreement that was included as part of the CID program … Science, medical product development, this benefits."

Although CBER has received only one CID submission so far, the pilot has had a positive impact on the types of submissions the biologics center is seeing outside of the program, Scott said.

At CBER, "what we have had is at least a couple dozen truly complex innovative proposals come in just under regular IND during this time, and I think part of that is this sort of increased era of openness and open discussion that the pilot program has helped promote," he said.

Expanding The Tent: Improving Trial Participation Among Under-Represented Patient Populations

BEN COMER

The biopharma industry has struggled to recruit patients into clinical trials that adequately reflect the diverse patient populations they hope to reach with new products. Failure to improve minority subgroup participation now will cost trial sponsors later.

- New Research from the Tufts Center for the Study of Drug Development reveals the extent to which minority groups are absent from clinical trials supporting new drug and biologic approvals.
- Additional tools are emerging to help sponsors effectively recruit and enroll underrepresented patient populations in clinical trials.
- Patient engagement approaches should be tailored to reflect the needs of specific patients and communities.

The strength and authority of science in society, such as it is, relies on a commonly held belief that scientific findings are objective and impervious to the biases of its practitioners. Scientific facts – including the way human bodies respond to medical interventions –

FDA's Drug Trial Snapshots
Section 907 of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) required the FDA to report on clinical trial diversity according to sex, age and race/ethnicity. The Drug Trials Snapshot program – which includes consumer-friendly information on drug uses, safety information, clinical trial participants and differences in sex, age and race/ethnicity for newly approved NMEs and original biologics – was established in 2014. The stated goal of the program is to make demographic information about participants in pivotal clinical trials more transparent. As of 12 March 2020, there were 243 products covered in Snapshots.

must be recognized and trusted as facts, until new studies and experiments come along to update the old facts or replace them. Identifying and controlling for variables during a clinical study is a key principle of the scientific enterprise, one that distinguishes rigorous and actionable conclusions from studies that distort reality, lead to poor policy decisions, or worse.

All studies have limitations, whether they are acknowledged or not: human biology, including the function of roughly 20% of proteins in the body, for example, remains a mystery. The mechanism of action for many drugs used to treat central nervous disorders, for another example, are not well understood. And yet, scientists and clinicians have uncovered important distinctions between individuals across ethnicity, gender and age groups, and how they respond differently to specific medications. In the race to bring new treatments and vaccines to bear on COVID-19 infections across the globe - and across ethnic groups - trial sponsors should make sure these distinctions are sufficiently elucidated, and communicated to physicians.

What is surprising – or perhaps not, from a historical perspective – is that in 2020, minority groups remain woefully underrepresented in FDA-regulated clinical trials. Of the six new molecular entities (NMEs) approved by the FDA between 1 January 2020 and 26 February 2020, five did not have enough non-white participants in supporting clinical trials to determine differences in response or side effects, according to the FDA's Drug Trial Snapshots.

Numerous studies have shown that differences often do exist, beyond well-known examples of blood thinners or hypertensive agents. Of the 167 NMEs approved between 2008 and 2013, 35 (roughly one-fifth) contained product labeling about race or ethnic differences in pharmacokinetics, safety, efficacy or pharmacogenetics, according to research cited by the Office of Minority Health in a 2016 presentation to Congress.

Baseline For Improvement

Despite years of FDA effort and goading to improve minority inclusion rates, obstacles remain. New research from the Tufts Center for the Study of Drug Development (CSDD), led by Ken Getz, professor and deputy director, provides a deep analysis of participant diversity – or lack thereof – in clinical trials supporting new drug approvals between 2007 and 2017. The findings cast the issue in stark relief. "It's the first study that I'm aware of that actually quantifies the magnitude of disparities and underrepresentation in clinical trials across nearly all therapeutic areas," said Getz. "Evidence supporting efficacy and safety of new therapy is not definitive evidence when we don't have representation of the full community of patients who are going to receive that treatment."

"Evidence supporting efficacy and safety of new therapy is not definitive evidence when we don't have representation of the full community of patients who are going to receive that treatment." – Ken Getz

The problem with the FDA's Drug Trial Snapshots program, said Getz, is that it "doesn't give us any information about disease prevalence, and it tells us nothing about whether the demographic distribution,

EXHIBIT 1

Overall Disparities For NDAs And BLAs Approved Between 2007 And 2017 (n=341)

	Female	Male	White	Black	Asian	Hispanic / Latino	Other
Total participants	469,919	532,628	552,868	40,265	75,134	44,732	19,782
Distribution of Total Participants	46.9%	53.1%	75.4%	5.5%	10.3%	6.1%	2.7%
Predicted Level of Participation (based on census and disease prevalence)	506,734	490,793	508,468	86,694	34,402	57,839	54,356
Predicted Distribution	50.8%	49.2%	68.5%	11.7%	4.6%	7.8%	7.3%
Difference	-36,815	+41,835	+44,400	-46,429	+40,732	-13,107	-34,574
Disparity Percentage*	**-7.3%**	**+8.5%**	**+8.7%**	**-53.5%**	**+118%**	**-22.7%**	**-63.6%**

SOURCE: TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

*DISPARITY PERCENTAGE IS THE 'DIFFERENCE' DIVIDED BY PREDICTED LEVEL. SHADED CELLS INDICATE WHERE DATA IS NOT AVAILABLE.

given individual disease prevalence variation, is even representative." The results of the Tufts study, titled *Assessing Participant Disparities in Clinical Trials Supporting New Drugs and Biologics Approved between 2007 and 2017* and supported by a grant from Merck & Co., reveal "data showing substantial underrepresentation of black participants - and to a lesser extent Hispanic participants — in clinical trials" during the 10-year period, said Getz.

The objectives of the CSDD study, which was shared with *In Vivo*, are threefold:

- to assess the availability and disclosure of participant demographic subgroup data provided by pharmaceutical and biotechnology companies to promote greater transparency and accuracy in future assessments of participant diversity;
- to rigorously gather data to inform a baseline assessment of the magnitude of participant demographic subgroup disparities in clinical trials of new drug approvals and ultimately identify opportunities to improve minority underrepresentation and access to investigational treatments; and
- to establish and convey an approach that the FDA – and others in the public and private sector – can apply and adapt to improve the value of the Drug Trial Snapshot program and other disclosure initiatives informing the general public and stakeholders in the clinical research enterprise.

To understand the level of subgroup underrepresentation in trials, the CSDD team compared trial participant demographic data supporting new drugs and biologics during the 10-year period with corresponding disease prevalence rates, and when that was not available, to US census data. For each approved product, CSDD developed a "disparity percentage" representing the difference between the actual number of trial participants by subgroup, and the predicted, or expected, number of participants by subgroup based on prevalence or US census data during the year of the drug approval. That number was then divided by the predicted number to get the disparity percentage (*see Exhibit 1*).

The highest overall levels of underrepresentation, according to the data, were among black/African

EXHIBIT 2

10-Year Average Disparities By Therapeutic Area For Approved NDAs And BLAs (N=341)

Figures reflect the percent of drugs within a T.A. which had a disparity of greater than -20%*	Female	Male	White	Black	Asian	Hispanic / Latino	Other
Oncology	26.4%	27.9%	3.7%	65.4%	20.0%	100.0%	30.4%
Neurology	45.8%	0.0%	11.1%	100.0%	66.7%	75.0%	100.0%
Cardiology / Vascular Disease	30.0%	5.0%	0.0%	66.7%	75.0%	60.0%	
Endocrinology	50.0%	0.0%	0.0%	33.3%	0.0%	33.3%	0.0%
Infections and Infectious Disease	0.0%	6.7%	8.3%	83.3%	50.0%	44.4%	0.0%
Dermatology	60.0%	20.0%	0.0%	100.0%		0.0%	
Gastroenterology	0.0%	0.0%					
Pulmonary / Respiratory Disease	40.0%	0.0%	0.0%	100.0%		50.0%	66.7%
Psychiatry	20.0%	0.0%	25.0%	50.0%		100%	
Rheumatology	0.0%	30.0%	0.0%	100.0%	100.0%	100.0%	50.0%
Immunology	85.7%	0.0%	0.0%	100.0%	0.0%	60.0%	100.0%
Ophthalmology	25.0%	25.0%	20.0%	60.0%	0.0%	25.0%	100.0%
Musculoskeletal Disease	50.0%	50.0%	0.0%	100.0%			
Hematology	0.0%	0.0%					
Urology	60.0%	40.0%	0.0%	100.0%			
Nephrology	0.0%	0.0%	0.0%	50.0%	50.0%	100.0%	0.0%
Hepatology	0.0%	100%					
OB/GYN	0.0%		0.0%	0.0%		100.0%	

SOURCE: TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

descent (-53.5%), Hispanic/Latino (-22.7%) and "other" (63.6%) participant subgroups; the "other" category includes Native American, Native Alaskan, and Hawai'ian or Pacific Islander participants. Overrepresentation among Asian participants in certain therapeutic areas may be due in part to market access requirements in key geographies including Japan and China, a reflection of the global nature of clinical trials.

Data completeness associated with approved products is another concern; reporting participant subgroup information in FDA-regulated drug development is optional, according to the CSDD study. On top of that, subgroup participation itself is not required, either. "The FDA does not have the regulatory or statutory authority to require that [trial] sponsors include demographic subgroups as

participants in their clinical trials," said Lola Fashoyin-Aje, Division of Oncology 3 acting deputy director at the FDA's Office of Oncologic Diseases, during an American Association for Cancer Research workshop held in Washington DC, on 13 February. "FDA can't legally go after sponsors who do not adhere to [FDA proposed] standards," she said.

Interestingly, minority subgroups were well represented in oncology trials between 2007 and 2017, with one glaring exception: Hispanic or Latino participants were markedly underrepresented, despite positive disparity percentage scores among all other races and ethnicities, according to the CSDD study (*see Exhibit 2*). Black participants, or participants of African descent, were underrepresented in roughly two-thirds (68.8%) of the therapeutic areas for which all new drugs and biologics were approved during the 10-year period. Hispanic or Latino patients were similarly underrepresented in 64.3% of all therapeutic areas. Women were notably underrepresented in both immunology and endocrinology therapeutic areas, as well.

Further Studies Draw Similar Conclusions

A collaboration formed in 2018 between RTI International, a non-profit research institute based In Research Triangle, North Carolina, and Project Data Sphere, an open-access research platform providing de-identified patient-level data from oncology clinical trials, is linking individuals in the national Medical Expenditure Panel Survey (MEPS) with trial data housed in Project Data Sphere. The intent of this project is to understand how representative cancer trial patients were with similar cancer patients in the general population. The linked results, which include data on sociodemographic and health-related characteristics, offers new insights into health disparities research. Among many findings in the initial linkages, researchers found that a cancer patient's likelihood of survival was associated with their insurance coverage status, their status as a smoker, their health preferences, and the amount of services received during outpatient visits with a physician. Lung cancer patients enrolled in clinical trials were more likely to be white, married and current smokers compared with similar patients in the MEPs database, according to a 2018 study published Frontiers in Oncology.

Disparities in the practice of medicine are not limited to clinical trial participation. A widely circulated study published by the *Proceedings of the National Academy of Sciences of the United States of America* in 2016 found that many white, US-born medical students and residents did recognize differences between white and black ethnicities; unfortunately, the differences they recognized were false and racially biased. Examples of "false belief items" presented to students and residents as part of the study included "blacks have denser, stronger bones than whites," "blacks' nerve endings are less sensitive than whites," and "blacks' skin is thicker than whites," among others. Approximately 50% of the medical students and residents participating in the study reported that at least one of the false beliefs was possibly, probably or definitely true, according to the study, and participants agreed with 11.55% of the false beliefs, on average. The study's authors concluded that "many white medical students and residents hold beliefs about biological differences between blacks and whites, many of which are false and fantastical in nature … these beliefs are related to racial bias in pain perception."

Prescribing physicians, regardless of ethnicity, may also lack awareness of – or easy access to – drug information related to minority subgroup safety and efficacy information. A study published last September in *Pharmaceutical Medicine* found that between 2008 and 2012, 96% of new chemical entities supported by large-scale clinical trials and registered in both the EU and Singapore contained safety issues specific to ethnic subgroups in their registration dossiers. However, ethnicity-specific safety information was only present in 48% of European public assessment reports, 32% of the European Union summaries of product characteristics, and 36% of the Singapore package inserts for the same products. As a result, the information is often unknown to prescribers in Europe and Singapore, according to the study authors.

Tools For Improving Trial Diversity

Last June, the FDA released new draft guidance for the biopharma industry on "enhancing the diversity of clinical trial populations," with recommendations including:

- expanded eligibility criteria to better reflect all of the patients likely to use a drug; characterizing drug metabolism early in the clinical process, across patient groups that may metabolize a drug differently;
- making trial participation less burdensome for patients by reducing frequency of clinical visits;
- emphasizing remuneration for travel, lodging and other expenses;
- ensure that trial sites include areas with higher numbers of racial or ethnic minorities;
- use mobile and digital tools, including biometric sensors, to replace site visits and produce real-time data for investigators; and
- engage with patient advocacy groups on trial designs and protocols, especially in rare disease studies, among other recommendations.
- The guidance also references the importance of public outreach and communication, which can be challenging if the needs and cultural makeup of specific communities are not well understood.

Other groups are also taking steps to improve clinical trial diversity. In the UK, Manchester-based Christie NHS Foundation Trust, a leading cancer center in Europe, partnered with clinical trial recruitment company Innovative Trials to improve black, Asian and local minority ethnic community member participation in cancer studies. Andrew Wardley, consultant medical oncologist at The Christie and project lead for the initiative, said that the partnership "is about building the structures that allow people to make decisions about clinical trials and give them the information in a very supportive way, which is often not as optimal as it might be." (*Also see "Interview: UK Initiative Bids To Boost Access To Cancer Clinical Trials" - Scrip, 9 Mar, 2020.*)

Indeed, traditional marketing and advertising channels may not be an effective way to recruit patients from diverse populations into clinical trials, since they often lack the nuance and educational value needed to adequately explain the benefits and risks of trial enrollment. An increasing number of health systems that conduct trials have begun using patient navigators to help with recruitment efforts. These patient navigators focus on providing high-touch, often in-person engagement with potential trial participants. Large providers of electronic health records systems (EHRs), such as Epic and Cerner, are offering "clinical decision support" based on information housed in the EHR. For example, a patient coming in for a doctor's appointment can trigger a notice to the physician about available trials matching the patient's profile. Once identified, a patient navigator "can greet the patient at their point of care, and if that particular patient is appropriate for a trial, they can walk them over to the trial office and introduce them to the personnel there," said Getz. "This high-touch approach holds a lot of promise." In rare diseases such as lupus, for example, where the prevalence is higher among minority populations, navigators are moving within church systems and community centers, where people congregate, according to Getz.

Rare Disease Recruitment

Locating and recruiting a diversity of patients into clinical trials for rare diseases can be especially challenging and time consuming, given the small number of patients globally. In addition, the study of genetic variants and their relationship to rare diseases is typically accessed and analyzed through large global data banks, which skew dramatically toward Caucasians of European ancestry, said Arndt Rolfs, CEO of Centogene, a Rostock, Germany-based rare disease company focused on identifying causal gene variants and biomarkers. According to a 2016 study in *Nature*, of the 2,511 genome-wide association studies and 35 million samples collected in 2016, 81% were collected from individuals of European ancestry. "Researchers rely on these databanks despite an obvious bias, even though it's clear that there's a big difference, just in the genetic layer, if we're comparing the genome in an

individual coming from Japan, Mongolia, New Zealand or Germany," for example, said Rolfs.

Centogene, which also markets a range of diagnostics and genetic sequencing services, has compiled its own databank and technology platform comprised of genomic, proteomic and metabolomic data from over one million patients. "Roughly 20% of those patients are from the Middle East, 15% are from Latin America, 15% are from North America, 20-25% are from Europe, and the remaining 20-25% are from Asia, New Zealand and Australia," said Rolfs. The company is also currently enrolling patents in 48 observational, non-interventional clinical studies, according to *Clinicaltrials.gov*, to "get a natural history documented from the individual patient on the one hand, and also to develop new biomarkers," he said.

The databank and technology platform can help partners locate and recruit patients faster, notes Rolfs, citing a collaboration with San Francisco-based Denali Therapeutics announced in October of 2018. Denali is developing treatments for a subtype of Parkinson's disease, based on targeting the LRRK2 gene. "Denali had a developmental plan for the recruitment of 500 patients, and had expected to need five years to identify these 500 patients that demonstrate specific mutations within the LRRK2 gene," said Rolfs. "They contacted us, we entered the information into our databank looking for activity in our network, and we immediately identified 3,500 patients globally. So instead of investing money and time identifying patients over the next five years, we have been able to significantly speed up the recruitment of patients for the clinical program." Through an initial consenting process, Centogene is able to contact the physicians of specific patients directly about trial enrollment opportunities.

Patient Attitudes Toward Trial Participation

When discussing clinical trials and the need to recruit more minority participants, it is inevitable that the Tuskegee syphilis study atrocity, or the fact that Henrietta Lacks' cells were stolen without consent, will be mentioned as a contributing factor for mistrust in black communities. That may be true; however, a new global survey from the Center for Information and Study on Clinical Research Participation (CISCRP), a nonprofit focused on educating the public about clinical research, suggests that members of the black community who decided to participate in a trial were significantly less likely than any other subgroup to hear about the trial from a general practitioner or specialist, suggesting a failure by physicians to educate and provide referrals for black patients. Among black trial participants, 8% learned about a trial from their physician, and 20% learned about a trial from an online government database. By comparison, 16% of participants across all ethnicities learned about a trial from their physicians, and 12% learned about trials from an online government database.

Moving all or part of a clinical trial out of the traditional site and into the home, and using concierge services and technology, holds promise for engaging underserved populations, according to the CISCRP survey. Asked about preferences related to visiting a study site versus collecting data at home, 75% of the total respondents (n=12,451) said collecting all study data themselves, at home, was appealing; 79% said nurses traveling to their homes for all study visits was appealing; and having a mix of home and clinical site visits was appealing to 73% of respondents. Forty percent of black respondents found home visits from a nurse to be "very appealing," compared with 24% of respondents identifying as Asian. Women were also more likely to find home visits from a nurse, and home data collection "very appealing," compared to male respondents. Asked about the importance of clinical research in the discovery and development of new medicines, respondents identifying as black, and respondents identifying as white, were more likely to feel that clinical research is "very important" compared to other subgroups.

Educating and engaging patients – across all patient populations – will become increasingly important for drug developers, and for patients themselves. With a raft of gene therapies and other expensive specialty medications filling biopharma pipelines, payers have indicated their intent to limit coverage for patient subgroups when clear safety and efficacy is not available.

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