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Thirty-six drugs and devices were approved or entered a new trial phase last week.

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Digital Therapeutics Sector Projected to Grow Exponentially

By James Miessler

As the digital therapeutics/software as a medical device sector continues its significant growth, clinical trials for the products are projected to expand logarithmically.

The space is seeing a big transformation from merely following patient symptoms to serving as interventions in a growing number of areas, according to Mark Opler, chief resource officer for directing research and development at WCG MedAvante-Prophase.

"This used to be, I would say, almost a fringe category of potential treatments. It's moved considerably from symptom tracking to intervention," Opler told *CenterWatch Weekly*. "There is an ever-widening array of conditions and symptoms that digital therapeutics are intended to treat. Mood disorders, particularly depression, anxiety, those have been traditionally thought of as the core target categories for digital therapeutics, but as time goes by, we're seeing applications to psychosis, to trauma and to other diseases, including attention deficit and related conditions."

The FDA has already approved a number of digital therapeutics products. These include Akili Interactive's EndeavorRx, an ADHD videogame treatment for children, NightWare's self-titled product that uses an AppleWatch and iPhone to disrupt nightmares without disturbing sleep and a trio of Pear Therapeutics apps for chronic insomnia, opioid use disorder and substance use disorder.

see **Digital Therapeutics** on page 4 »

Ask the Experts: Setting the Data Monitoring Committee Up for Success

This monthly feature presents a variety of questions from clinical trial professionals with answers from WCG's expert staff. This month features Matt Downs, a statistical scientist with WCG Statistics Collaborative.

Question: How important is the first data monitoring committee (DMC) organizational meeting and when should it occur?

Answer: For a DMC, that first organizational meeting sets the stage for the DMC's future data reviews. It should occur prior to recruitment and have a robust agenda.

I like to use the analogy of a boat in a port: before you set sail, you want to make sure you're headed in the right direction. You're going to plot your course and check the navigational devices before heading out to the ocean. That's why the organizational meeting needs to take place before recruitment begins. This meeting is the last chance for the DMC to identify potential trial obstacles and offer feedback while its members are still naïve to the study data. Any requests after the DMC begins to review data will make sponsors wonder, "What's really going on? What's behind that question?" It's much cleaner to be able to have those discussions before the DMC has seen interim data.

There's another reason to meet before recruitment begins: some potential DMC members will refuse to serve because holding the organizational meeting post-recruitment suggests that the sponsor doesn't have its safety monitoring process fully established.

see **Ask the Experts** on page 5 »

Upcoming Events

15 FEB — CONFERENCE
Successful Strategies for Digital Health in 2022: Who's Doing Digital Well and How You Can Get Started

29 MAR — CONFERENCE
Data Integrity for GCP Professionals: *Core Requirements, Expectations and Challenges*

1 MAY — CONFERENCE
MAGI's Clinical Research Hybrid Conference — 2022 East

[VIEW ALL EVENTS]

Industry Briefs

Califf Lays Out Focal Points for FDA if Confirmed to Lead It

While waiting for the Senate to schedule a vote on his nomination to be the next FDA commissioner, Robert Califf is busy articulating what his priorities will be once he's confirmed.

Industry experts are also debating what he will focus on, with some expecting that he will make reforming clinical trials his top priority.

Califf last week provided two senators a deeper look into the agenda he would set at the helm of the agency, including using real-world data (RWD) and real-world evidence (RWE) in trials, how trials should be conducted for software as a medical device (SaMD) and innovative trial designs.

In letters to Sens. Mike Braun (R-Ind.) and Robert Marshall (R-Kan.), Califf expressed interest in developing an improved system for generating post-market trial data and pointed to several RWD/RWE initiatives at the agency that have already produced positive results, including a March 2021 report detailing 90 instances of RWE being used to inform regulatory decisions for a range of medical devices. He also noted the four draft guidances the agency recently issued on using RWE in trials.

Califf also intends to ensure that the agency keeps pace with the advances being seen in the digital health technology and SaMD spaces, particularly how trials can be done effectively for them and noting the importance of the FDA's Digital Health Center of Excellence in these efforts and his eagerness to further them.

And speaking during an FDAnews webinar last week, panelist Nancy Myers, CEO of Catalyst Healthcare Consulting and moderator/panelist Wayne Pines, president of healthcare at APCO Worldwide, agreed that Califf will push for a greater use of RWE and the expansion of clinical trial size.

While the pair believes that he would immediately focus on clinical trial reform should he get confirmed, Myers also noted the challenges he would be up against as commissioner that he would have to navigate.

In particular, the new agency head will have to deal with increased scrutiny of the FDA drug approval process while contending with employee burnout after two years of relentless work during the public health emergency.

She referenced controversial agency decisions, such as the approval of Biogen's Alzheimer's disease therapy Aduhelm (aducanumab) in June 2021 and Sarepta Therapeutics' Duchenne muscular dystrophy (DMD) drug Exondys 51 (eteplirsen) in 2016, which occurred under Califf's first stint as FDA commissioner from 2016 to 2017.

Another presenter, David Fox, partner at law firm Hogan Lovells, also touched on the perception that FDA approvals are not always based on adequate data.

"When you issue 50 approvals a year, how do you walk a straight line?" Fox asked, noting the challenges of having a one-size-fits-all approach to approving dozens of new drugs. He said the agency "has to become better" at articulating what type of data are actually used to support approvals in order to build public confidence.

Sens. Braun and Marshall were among a bipartisan group of eight lawmakers who did not vote for Califf during a Senate committee's consideration of his nomination.

Read the responses to Braun here: https://bit.ly/3FNk7sY.

Read the responses to Marshall here: https://bit.ly/3lltqCj.

Analysis: DCTs Are Proving Their Benefits, Significantly Cutting Down Trial Costs

Decentralized trials (DCTs) can provide up to 14 times return on investment for phase 3 trials due to accelerating trial timelines, a new Tufts study has found.

In phase 2 trials, DCTs typically saved one to three months' worth of time and delivered a net benefit up to five times greater than investment costs.

"On average, the financial returns to drug sponsors from shorter development times, lower clinical trial screen failure rates and fewer clinical trial protocol amendments associated with DCTs substantially exceeded the costs of investing in DCT technologies," said Joseph DiMasi, director of economic analysis at Tufts' Center for the Study of Drug Development (CSDD).

The study analyzed data from more than 150 DCTs on the Medable platform using an expected net present value based on trial cycle time, cost and performance benchmarks, in addition to some conservative assumptions about the impact of DCTs and their investment costs.

CSDD has declined to release detailed data from the study prior to it undergoing peer review. When peer review is complete, Tufts will share detailed findings on the financial savings DCTs can provide.

FDA Shares Examples of Complex Clinical Trial Designs

In its effort to ramp up the use of complex innovative designs (CID) in late-stage research, the FDA has published three study designs it considers novel.

Through its CID Pilot Meeting Program, the FDA has issued case studies on a proposed master protocol to study chronic pain, a proposed systemic lupus study that uses an adaptive rule to consider changing the primary endpoint 52 weeks into the study and a proposed diffuse B-cell lymphoma trial that uses external control data.

The program is designed to advance the use of complex adaptive, Bayesian and other novel designs. Sponsors that

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Industry Briefs

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participate in the program will be able to interact more closely with agency staff on their proposed innovative designs. The agency has set four requirements for participating in the pilot study, which continues through 2022:

- The sponsor must have an IND or pre-IND number for the medical product in the CID proposal;
- The proposed CID must intend to gather substantial evidence of effectiveness to support regulatory approval;
- The trial cannot be a first-in-human study and there must be an adequate amount of clinical information to inform the proposed CID; and
- The sponsor and agency must be able to agree on trial design information to be shared publicly.

Read the case studies here: https://bit.ly/3Kj3Boe.

EU Begins Initiative to Improve Its Clinical Trial Landscape

The European Commission (EC) has begun a new initiative to improve the way clinical trials are conducted and to better integrate clinical research into the European health system.

The initiative, Accelerating Clinical Trials in the EU, outlines key goals, including facilitating innovative trial approaches, helping to modernize good clinical practice, spurring more multinational trials in the trade bloc and refining ethical oversight.

The initiative also intends to encourage and support better trials for rare diseases, unmet needs and vaccines/therapeutics for pandemics and public health emergencies. The newly launched initiative will be conducted alongside the EU's Clinical Trials Regulation and its database component, the Clinical Trials Information System, which take effect Jan. 31.

Clinical Research Trio Comes Together as Centricity Research

Three prominent clinical research organizations that joined forces near the end of 2021 have unveiled their new name: Centricity Research.

LMC Manna, IACT Health and True North Clinical Research merged last year to create a combined network of more than 40 sites, 1.5 million patients and 150 active investigators across the U.S. and Canada.

Centricity Research offers expertise in a range of therapeutic areas, including infectious disease, neurology, oncology, cardiology, dermatology, endocrinology, vaccines and women's health, and claims to be the largest consolidated research network in North America.

Digital Therapeutics

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Digital therapeutics can also be developed to serve as coaching tools to help improve certain behaviors. While some are intended to serve as standalone products, others are being developed for use in combination with drugs or other medical devices. The sector's growth is predicted to grow to $12.1 billion by 2026.

Because patients are using a piece of software, not simply taking a drug, determining what will be used as the placebo can be a taller order. Some companies come up with "inactive," nontherapeutic software to serve as the placebo, while others develop games or use treatment as usual for patients in the placebo control group.

But according to Opler, it may be more fruitful to concede that this method of blinding "may be on some level challenging, if not impossible" and go another route: using an evaluator that has as few ties as possible to the trial beyond assessing patient symptoms, an avenue for blinding that's gained greater traction in digital therapeutics trials.

"What's transpired instead when you want to evaluate efficacy in an objective way in a digital therapeutics study is to have a fully independent and blinded evaluator, someone who is blinded as much as possible to the treatment and the study design, and whose only contact with the patient is evaluating their symptoms," Opler said. "It's tough to find the sugar pill equivalent in a digital therapeutics trial. Blinding the evaluator, keeping them independent from other aspects of conduct of the study, is another route to ensuring that the evidence we gather is rigorous and will be acceptable to the larger community."

Endpoints are another big issue for digital therapeutics trials, according to Dave Hanaman, president and chief commercial officer of Curavit, a virtual CRO.

According to Hanaman, many companies are using new ways of collecting endpoints, and in some cases new endpoints altogether; because of this, the challenge they face is that their trial results may be considered unsuitable for comparison with prior studies.

"They run into the problem that it's potentially not comparable or they leave themselves open to being challenged that their results, while good, can't be compared to some gold standard trial that was done 20 years ago," he said. "That's where developing new endpoints, being thoughtful about it and then often comparing them to traditional endpoints, that seems to be the long pole in the tent for digital therapeutics companies. That's the thing they really have to pay attention to."

In Opler's opinion, while existing measures can and certainly should be improved upon and new measures validated as scientific understanding of different diseases continues to progress, that progression, not the challenges of implementation, should be the impetus.

"It's always important to ensure that the endpoints we're using are valid and reliable. However, we also need to be careful not to hold digital therapeutics necessarily to a completely different standard than we would hold drug treatments," he said. "Just because it's difficult to use a traditional measure in a digital therapeutics study, it's not an excuse or a meaningful rationale. It's not a good reason to abandon traditional assessment. There are lots of good reasons to improve on traditional measures and to validate new ones, but 'it's hard' is not one of them. I fully agree with the sentiment that we need to improve on our existing measures, but I think our reasons for doing so in digital therapeutics have to be very carefully thought out."

Digital biomarkers can certainly be beneficial in clinical trials, including those for digital therapeutics, but they aren't yet at the stage where they can serve as substitutes for established primary endpoints, Opler said. In the future, they are bound to become more acceptable and widely used as sources of safety and efficacy data due to rising attention and interest from industry, but it's important that their adoption in digital therapeutics trials "be on the basis of significant evidence rather than as a matter of convenience," he said.

As it stands, digital biomarkers require further identification and clinical validation, though they are used in clinical trials, and both pharma and academia have recognized that this will take large collaborative efforts and significant financial investment.

Case in point: as of this writing, the FDA has not received a single digital biomarker submission for evaluation under its Biomarker Qualification Program. Further, Brinnae Bent and other researchers wrote in a July 2020 article in the *Journal of Clinical and Translational Science* about the need to come together on the development and validation of digital biomarkers.

"Currently, digital biomarker development processes are siloed, resulting in numerous studies with digital biomarkers that are not validated properly or are duplicates of already existing digital biomarkers," they wrote. "Open-source digital biomarker development is necessary to broaden the validation of digital biomarkers, reduce duplication and expedite innovation."

But huge growth is anticipated in the realm of digital biomarkers, and Opler is certain it's a matter of "when, not if, they become more acceptable and more widely utilized."

While digital therapeutics are well-suited for decentralized trials (DCTs), it's very important to consider the patient population at the center of the trial. For instance, although a majority of evaluations and data collection likely can be done remotely, keep in mind that some measurements are best done in-person, usually for safety reasons. Some physical signs and symptoms, such as stiffness and rigidity, for example, aren't optimally assessed by video or other remote mediums; this is especially true in neurology, Opler said.

In addition, Hanaman highlighted other key questions that need to be asked when designing and conducting a trial for a digital therapeutic product, including what patients to enroll, how comfortable patients are with remote engagement/the digital therapeutic, how to verify protocol adherence and whether the protocol ensures the safety of participants.

Ask the Experts

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Q: How should I begin planning the meeting and how should it be held?

A: To get started, you'll need an agenda that includes a review of past trials, the study design and the template for the interim reports the DMC will review. And, although it may change because of enrollment, you want to give thought to scheduling the date of the first data review meeting.

Ideally, this first meeting should be in person. Yes, that makes scheduling difficult, but keep in mind most DMCs will be working together for years. It's useful to meet the other committee members and sponsor representatives — and the independent statistical team that will be preparing interim reports.

Q: What are the most important questions to address with the DMC?

A: It's important to hash out the following with the DMC early on:

- Will the DMC have access to efficacy data? This is one of the stickiest issues that comes up. It's best to address it at the organizational meeting. The DMC members must have the ability to access efficacy data, even when reviewing only safety, because they need the ability to assess risk vs. potential benefit;
- How current will the data be? Too often, this topic gets overlooked, but DMCs need to know — if for no other reason, to control expectations;
- What is the level of masking? Determine the level of masking the DMC expects in its closed reports. Interim DMC reports often semi-mask the treatment groups with labels such as "Group A" and "Group B." Sometimes, committee members will feel that the DMC should only know the true identity of the treatment upon request if needed given the emerging data. However, we generally recommend that DMC members should be aware of the treatment group identities corresponding to the semi-masked labels at the DMC's very first report;
- How will the DMC handle futility/overwhelming efficacy? State in the charter whether one of the DMC's charges is to consider a recommendation for trial termination due to futility or overwhelming efficacy. If this isn't part of the DMC's charge, the sponsor should explain why during this first meeting; and
- Can the DMC hold unscheduled meetings? The charter should give the DMC the authority to conduct unscheduled meetings without notifying the sponsor. For instance, if the DMC sees a potential emerging safety signal, it may choose to meet sooner than the next planned meeting.

It's also important to conduct a thorough review of the protocol. DMC members will often freely give you their opinions on your study design. It is also a time to review prior studies for this and other indications. What do you know about the existing safety profile of the drug? This gives committee members a sense of what to expect and the ability to recognize if there is a new safety issue that wasn't uncovered from prior studies.

Q: How should communication flow between the DMC and the sponsor?

A: We encourage all study communication between the DMC and sponsor to go through the Statistical Data Analysis Center (SDAC), which can make sure all messages are appropriately routed. Think of it as a firewall. The SDAC goes by various names, but the task is the same: it prepares and presents the safety and efficacy reports for the DMC's reviews at their interim meetings.

An SDAC statistician … will attend the DMC meetings and have access to unmasked data. As an independent organization, it has no vested interest in the outcome of the trial. Usually, at least two other statisticians will be participating: the DMC statistician, who is a member of the DMC and typically sees unmasked data, and the trial statistician, who typically has access only to masked data that are pooled over treatment group.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
AN2 Therapeutics	Epetraborole	Nontuberculous mycobacterial lung disease	IND approved by the FDA
Ascletis Pharma	ASC22 (envafolimab)	Chronic hepatitis B	IND approved by the FDA
CytomX	CX-904	Advanced solid tumors	IND approved by the FDA
Green Valley Pharmaceuticals	Oligomannate (GV-971)	Alzheimer's disease	IND approved by the FDA
Jacobio	JAB-2485	Advanced solid tumors	IND approved by the FDA
Kinnate Biopharma	KIN-3248	Intrahepatic cholangiocarcinoma and urothelial carcinoma	IND approved by the FDA
Neurophth Therapeutics	NR082 (rAAV2-ND4)	Leber hereditary optic neuropathy associated with ND4 mutation	IND approved by the FDA
Palleon Pharmaceuticals	E-602	Solid tumors	IND approved by the FDA
PolarityTE	SkinTE	Chronic cutaneous ulcers	IND approved by the FDA
AB Science	Masitinib	Severe mast cell activation syndrome	Approval for a phase 2 trial granted by France's regulatory authority
Akeso	Ligufalimab (AK117) plus ivonescimab (AK112)	Advanced malignant tumors	Approval for a phase 1b/2 trial granted by China's regulatory authority
Clairvoyant Therapeutics	Psilocybin	Alcohol use disorder	Approval for a phase 2 trial granted by Canada's regulatory authority
Evaxion Biotech	EVX-01 in combination with Keytruda	Melanoma	Approval for a phase 2 trial granted by Australia's regulatory authority
Jiangsu Recbio Technology	ReCov recombinant two-component COVID-19 vaccine	COVID-19	Approval for a phase 2/3 trial granted by the regulatory authority of Philippines
Trials Initiated			
Angel Pharmaceuticals	CPI-818	Relapsed/refractory T-cell lymphomas	Initiation of phase 1/1b trial in China
HutchMed	HMPL-653	Advanced/metastatic solid tumors and tenosynovial giant cell tumors	Initiation of phase 1 trial in China
Arecor Therapeutics	AT247	Type 1 diabetes	Initiation of phase 1 trial
Profound Medical	TULSA Procedure	Prostate cancer	Initiation of phase 1 trial
SparX Group	SPX-101	Tumors	Initiation of phase 1 trial
Revelation Biosciences	REVTx-99	Allergic rhinitis and chronic nasal congestion without polyps	Initiation of phase 1b trial in Australia
ESSA Pharmaceuticals	EPI-7386 in combination with enzalutamide	Metastatic castration-resistant prostate cancer	Initiation of phase 1/2 trial

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Drug & Device Pipeline News

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Company	Drug/Device	Medical Condition	Status
HOOKIPA	HB-200 in combination with Keytruda	1st-line advanced/metastatic HPV16+ squamous cell head and neck cancers	Initiation of phase 2 portion of phase 1/2 trial
Xilio Therapeutics	XTX202	Solid tumors	Initiation of phase 1/2 trial
Lynk Pharmaceuticals	LNK01001	Active ankylosing spondylitis	Initiation of phase 2 trial
Resverlogix	Apabetalone	COVID-19 treatment	Initiation of phase 2b trial
Eisai	E2814	Dominantly inherited Alzheimer's disease	Initiation of phase 2/3 trial
Vigeo Therapeutics	VT1021	Glioblastoma	Initiation of phase 2/3 trial
Approvals			
AbbVie	Rinvoq (upadacitinib)	Refractory, moderate-to-severe atopic dermatitis in patients 12 years and older	Approved by the FDA for new indication
Glenmark Pharma/ Glenmark Specialty	Ryaltris nasal spray	Seasonal allergic rhinitis in patients 12 years and older	Approved by the FDA
Pfizer	Cibinqo (abrocitinib)	Refractory, moderate-to-severe atopic dermatitis	Approved by the FDA
Amgen	Lumakras (sotorasib)	KRAS G12C-mutated positive, unresectable, advanced and/or recurrent nonsmall-cell lung cancer	Approved in Japan
argenx	Vyvgart (efgartigimod alfa)	Generalized myasthenia gravis	Approved in Japan
Galapagos	Jyseleca (filgotinib 200mg tablets)	Ulcerative colitis	Approved in the United Kingdom
Novavax	Nuvaxovid (NVX-CoV2373)	COVID-19 vaccine	Approved for provisional registration in Australia
Rockwell Medical Jeil Pharmaceutical	Triferic injection	Hemodialysis-dependent chronic kidney disease	Approved in South Korea
Vifor Fresenius Medical Care Renal Pharma	Tavneos	ANCA-associated vasculitis	Approved by the European Commission

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

Editorial Director: Beth Belton, 703.538.7641, bbelton@wcgclinical.com
Reporter: James Miessler, 703.538.7650, jmiessler@wcgclinical.com
Sales: Russ Titsch, 813.767.6463, russ.titsch@centerwatch.com