CenterWatch Weekly

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Sponsors Name RWD/RWE Top Opportunity Area in Clinical Research

By James Miessler

Pharma and biotech sponsors are increasingly following the FDA's lead in using real-world data (RWD) and real-world evidence (RWE) in clinical trials, according to a new survey asking about the most valuable resources for clinical trials.

In the PPD-commissioned state-of-industry survey of 152 pharma and biotech sponsors across North America, Europe and the Asia-Pacific region, 45 percent of respondents named greater use of RWD/RWE as a highly promising area in clinical research, with large companies citing it significantly more often (54 percent) than smaller companies (31 percent). And 59 percent of the sponsors said they're using RWD/RWE more and more in their drug development programs.

These results are in line with the FDA's growing acceptance of RWD/RWE in regulatory submissions. Commissioner Robert Califf himself has signaled that the leverage of RWE — which the agency defines as conclusions drawn from analysis of RWD — will be a priority for the agency in the years to come (*CenterWatch Weekly*, July 18).

RWE has seen broad adoption across all therapeutic areas, says Debra Schaumberg, PPD's vice president and global head of strategic development consulting, and there are a number of driving factors when it comes to their use in regulatory submissions.

"The use of RWE in the regulatory context is being led, in large part, by activity

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Clear and Complete Trial Master Files Key to Inspection Success

By James Miessler

When faced with an FDA inspection, sponsors, CROs and sites must be ready to present trial master files (TMF) that are up to date and give a comprehensive account of the study. And the most efficient way to ensure they are is to maintain a constant state of inspection readiness with a regular TMF review schedule.

What does it truly mean to be inspection-ready? According to Laura Wiggins, TMF services project manager at Just in Time GCP, it's being able to detail the full course of a trial through the TMF — to tell its tale and paint a clear picture of all that occurred during the study.

"We know that no study is ever perfect, but we want to be able to tell the story of your study," Wiggins said during a WCG webinar, where she provided tips on TMF inspections. "Inspection readiness is ensuring that the people, processes and evidence of trial conduct are present for regulatory review."

This concept of "inspection readiness" is critical and revolves around focusing on TMF quality, timeliness and completeness. Reviewing the TMF periodically to ensure it's being properly maintained — with documents organized, complete and readily accessible — is essential. It's a good idea to start these reviews by going down through the TMF map, or index, checking documents and ensuring all filing locations are accurate, Wiggins

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Upcoming Events

16 OCT — CONFERENCE
WCG MAGI's Clinical Research Conference 2022 West

19 OCT — WEBINAR
Real-World Evidence in Medical Product Submissions: What Regulatory, Compliance & Quality Professionals Need to Know

16 NOV — CONFERENCE
17th Annual FDA Inspections Summit

[VIEW ALL EVENTS]

Industry Briefs

FDA Shares Ethical, Trial Design Considerations for Pediatric Participants

The FDA has published draft guidance outlining an ethical framework for involving children in clinical trials of drugs and devices, as well as trial design considerations.

The guidance offers what the agency deems to be fundamental ethical considerations that come into play when children are involved in trials. For instance, the guidance offers IRBs direction on approving trials that intend to enroll children and ways to assess whether an intervention/procedure offers a prospect of direct benefit to them. It also describes risk categories for interventions/procedures that don't offer a prospect of direct benefit and methods to assess risks for those that do, in addition to other items.

The guidance also delves into trial design for both drugs and devices, covering general factors as well as specifics. Overall, trials that involve children "should be designed to maximize the amount of information gained and minimize the number of subjects involved," the guidance advises.

"Children need access to safe and effective medical products and health care professionals need data to make evidence-based decisions when treating children. However, children are a vulnerable population who can't provide consent for themselves and are afforded additional safeguards when participating in a clinical investigation," Dionna Green, director of FDA's Office of Pediatric Therapeutics, said. "The best way to provide children with safe and effective treatment options is by including them in clinical research and providing these additional safeguards to protect them during clinical trials."

The guidance shares a number of points to consider when designing trials that involve pediatric patients:

- Age and physiological maturity of the child;
- Natural history of the condition;
- The current severity of the condition in the child;
- The presence of other complicating conditions;
- The safety/effectiveness of the drug or device in older participants or safety/effectiveness expected based on other clinical/nonclinical studies; and
- The likely duration of drug or device use and its effect on the growth and development of the child.

The guidance distinguishes between the differing challenges of drugs and medical devices, noting that devices come with

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Industry Briefs

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different hurdles because of their varying applications and the range of technology they use.

For devices, the guidance advises sponsors to consider the available clinical data when putting a trial together and notes that trials for indications involving both adults and children may be able to be designed as a single pivotal trial that enrolls both groups. Doing this can reduce the burden of multiple trials and optimize sample sizes. The guidance also notes that in certain situations, expected benefit and safety can be derived without separate studies of each pediatric subgroup, although "every effort should be made to gather data that adequately address each targeted pediatric subgroup for the proposed indication."

Read the full draft guidance here: https://bit.ly/3SaRVHB.

Site Payments Still a Pressing Issue for Clinical Trials, Industry Agrees

Sponsors, CROs and sites themselves agree that delayed site payments are still a significant issue in clinical research — so significant that they identified it as the most important activity to address in a recent survey.

According to Greenphire's 2022 Market Trends Survey, which involved 510 site personnel and 274 sponsor/CRO reps from around the world, the majority of respondents believe it's critical for sponsors and CROs to streamline site payments and invoicing in order to improve their working relationships with sites.

The findings were overwhelming: 82 percent of site representatives said that they are negatively affected by delays in site payments from sponsors, while 85 percent said they would rather work with sponsors/CROs that invest in technologies that address site payment hurdles, such as systems that help with invoice creation, distribution and reconciliation.

Access the full survey findings here: https://bit.ly/3dB6zsC.

Nonprofit Calls Pfizer's Minority Fellowship Program Racially Discriminatory

Pfizer's minority fellowship program is discriminatory toward Whites and Asians, claims the nonprofit Do No Harm, a group of healthcare professionals, policymakers and patients dedicated to protecting healthcare from discriminatory ideology.

The lawsuit, filed in the U.S. District Court of the Southern District of New York on Sept. 15, alleges that Pfizer's nine-year Breakthrough Fellowship Program, which offers mentorship, internships, employment after undergraduate/graduate education and full master's program scholarships to Black, Latino and Native American students and early-career colleagues, is illegal on multiple fronts. Not only does it violate the Civil Rights Act, it violates the Affordable Care Act, New York state and New York City law, the group alleged.

Although Pfizer also has the Summer Growth Experience Program, a similar initiative open to applicants of all races, what that program offers "is nowhere as comprehensive as the Fellowship's investment in and commitment to the Breakthrough fellows, as [it] does not appear to offer opportunities for post-undergraduate/post-graduate employment or scholarship for master's programs," the group says.

Do No Harm is asking the court to temporarily block Pfizer from selecting the Fellowship's 2023 class, enforcing its current racial requirements and running advertising for the program with the current requirements. It also has asked the court to permanently bar Pfizer from "maintaining racially discriminatory eligibility requirements" for the program and requests that the court order Pfizer to instate racially neutral criteria.

In a statement provided to *CenterWatch Weekly*, Pfizer said that it is aware of the lawsuit and stands behind its program.

"Pfizer is an equal opportunity employer proud of its commitment to diversity, equity and inclusion as we strive to create a diverse workforce that represents the patients and communities we serve," the company added.

At the time of writing, Pfizer's website still listed meeting "the program's goals of increasing the pipeline for Black/African American, Latino/Hispanic and Native Americans" as a requirement.

Read the full complaint here: https://bit.ly/3C1Mt48.

RWD/RWE Top Opportunity Area

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within targeted therapies in oncology, as well as cell and gene therapies, rare diseases, in vitro diagnostics and infectious diseases, including COVID-19 and many other infections," she told *CenterWatch Weekly*. "These are areas in which clinical development paradigms focused on the traditional randomized trial are often challenged, and industry is increasingly recognizing the value of well-conducted RWE integrated into overall evidence packages for investigational products."

Sponsors are wielding RWD/RWE to improve their clinical trial designs and optimize protocols, perform health technology assessments and develop external control arms that support regulatory filings. RWD/RWE has also been used in label expansions and some late-stage trials that use more pragmatic designs, Schaumberg noted.

The use of RWE has been well established for supporting postmarket safety studies, but applying the strategy early in drug development and in product assessments throughout various trial phases is currently an evolving area, according to Seema Betigeri, executive director of global regulatory affairs at Merck, who spoke at the RAPS Convergence conference this year. The path forward in this area, she believes, is global harmonization of RWD/RWE programs by regulatory authorities to enable the most effective use of these data and spur greater innovation in drug development.

The FDA has provided significant direction in this space in recent times, issuing draft guidances just last year covering assessments of patient registries (*CenterWatch Weekly*, Dec. 6, 2021), electronic health records and medical claims data (*CenterWatch Weekly*, Oct. 4, 2021) and regulatory considerations for noninterventional studies that use RWD (*CenterWatch Weekly*, Dec. 13, 2021).

And the agency now appears intent on monitoring the extent of RWD/RWE use. This month, the agency published a final guidance that directs sponsors to identify certain uses of these data in their drug and biologic submission cover letters so that the agency can track their usage and gain a more complete picture of their role in regulatory submissions. Still, some researchers believe more guidance should be provided; Chinese researchers at the University of Macau, for instance, believe that more in depth RWE guidance on technical data specifications, special patient populations and diseases with unresolved needs should be developed, according to their article published in *Frontiers in Medicine* last year.

In the view of Anne Delaney, PPD's vice president of RWE, the use of RWD/

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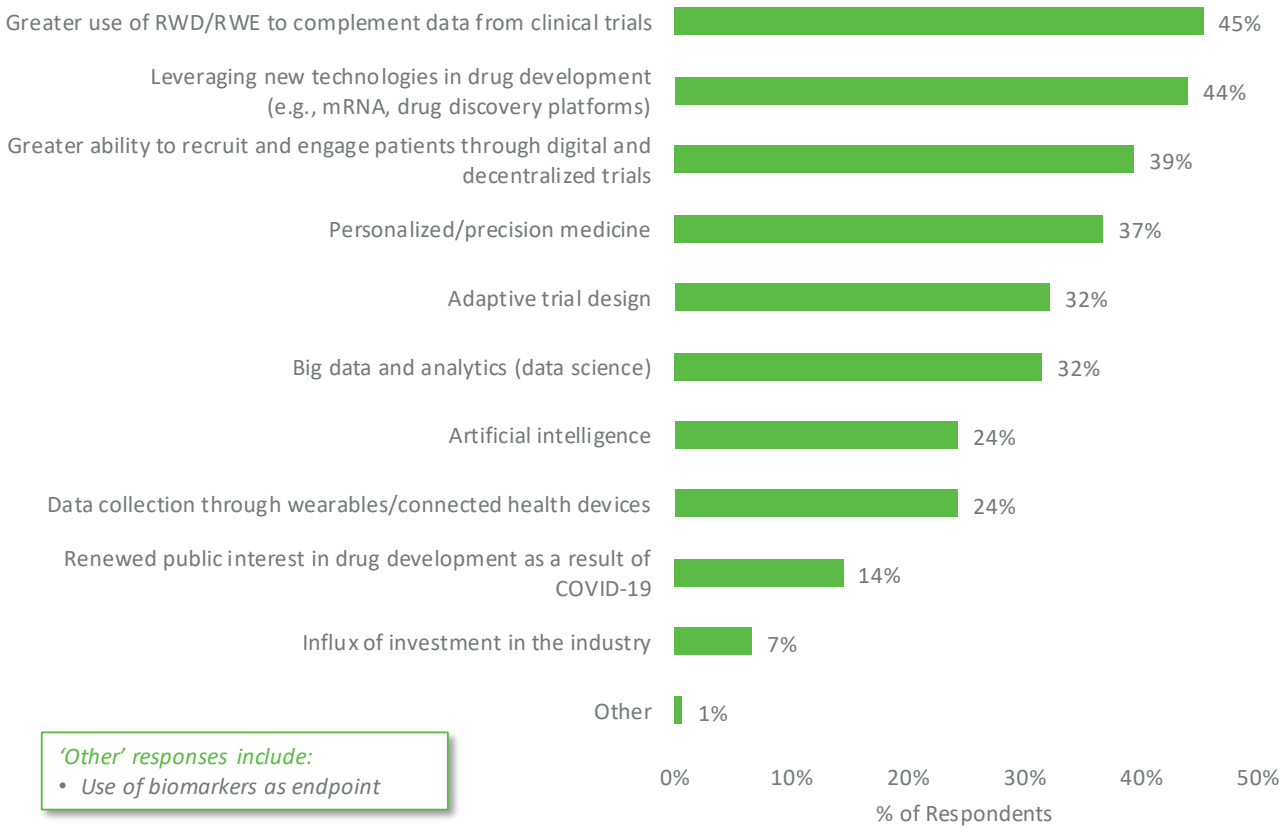
Top Areas of Opportunities in Clinical Trials



'Other' responses include:
- *Use of biomarkers as endpoint*

Source: PPD

RWD/RWE Top Opportunity Area

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RWE will continue its upward trajectory in the clinical research space and expand as time goes on and advancements continue to be made.

"A couple things will continue to drive wider uptake and acceptability of RWD/RWE: refinements in the RWD themselves (e.g., through directed deep curation), as well as technological advances to enhance access, connectivity and linkage to RWD, driving closer to the realization of a comprehensive patient view," Delaney said. "Additionally, we expect refinements and innovations in study design and analytical approaches grounded in epidemiological-first principles to produce high quality RWE."

"Continued integration of expertise in science, operations and technology will propel the breadth and depth of possibilities for RWD/RWE," she said.

Following RWD/RWE, 44 percent of survey respondents named new technologies in drug development, such as mRNA and drug discovery platforms, as a top opportunity.

In addition, 39 percent of respondents felt that the benefits conveyed by digital and decentralized trials on recruitment and engagement hold great potential, as does precision/personalized medicine (37 percent), adaptive trial design and big data/analytics (both 32 percent) and artificial intelligence (24 percent). What barely made the list, PPD said, were the influx of investments and public interest in clinical research spurred by the COVID-19 pandemic, which only seven and 14 percent of respondents named, respectively.

A majority of sponsor respondents are currently using the innovations, strategies and technologies they identified. More than half — 64 percent — said they're currently using adaptive trial designs, while 62 percent said they're employing digitalization (such as cloud computing, APIs and digital platforms) and 53 percent cited big data/analytics.

Half of these respondents said they're pursuing both decentralized trials and personalized/precision medicine, 47 percent said they're using wearables and connected health devices to gather data, 46 percent are pursuing genetic medicine (cell and gene therapies, RNA therapies, etc.) and just 33 percent said they're using AI.

Access the PPD survey report here: https://bit.ly/3SqvptV.

Read the FDA's recent final guidance here: https://bit.ly/2E0X69d.

Trial Master Files

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says. This is especially important because things can and do change throughout a trial, and certain documents may end up needing to be filed that weren't anticipated at trial start.

"Take your TMF map and walk through each zone. Go right down the line," she said. "Walking through that TMF map, you can take every artifact and really drill down, what did we have vs. what did we expect?"

For study team staff, for instance, you'll want to check and make sure that curricula vitae (CV) and training documents are filed for all employees, including any handover documentation (documents that explain the tasks and responsibilities of outgoing staff members to their replacements) as applicable. For the investigational product(s), all relevant documents and records should be filed and approved as required, while documentation for each lab involved in the trial, such as head of facility CVs, accreditations and so forth, should similarly be reviewed to ensure they're up to date, approved as required and present. And patient documents like logs and serious adverse event reports should be checked carefully to ensure they don't contain protected health information. These documents should also be cross-checked to verify that information, such as the number of randomized participants vs. number of participants visited at a site, all matches, Wiggins advised.

And every piece of information must be in the right place in the file. Challenges finding documentation are serious red flags in the eyes of the FDA and draw out inspections that could have otherwise gone much easier, notes Eric Pittman, program division director for the FDA's Office of Bioresearch Monitoring Operations. Thus, it would behoove sites and sponsors to have a well-organized methodology in place for maintaining their TMFs.

"A sign of the lack of preparedness for an inspection is the [organization's] difficulty in locating records needed," he said. "The lack of an organized system for records leads to additional questions and ultimately increases the time an investigator is on-site." (*CenterWatch Weekly*, May 6, 2019).

"A sign of the lack of preparedness for an inspection is the [organization's] difficulty in locating records needed."

—Eric Pittman, program division director for FDA's Office of Bioresearch Monitoring Operations

As part of a deep TMF review, also evaluate study plans, agreements, transfer of regulatory obligations, monitoring plans and oversight plans to ensure that they were truly followed.

Beyond reviewing the TMF intermittently, having a solid TMF plan is critical to achieving quality, completeness and timeliness, but problems will obviously arise if the plan isn't followed. A strong TMF strategy establishes the frequency of completeness reviews, filing timelines and responsibilities for filing documents, but it also establishes evidence. Some key things to consider include:

- Which SOPs were followed and if there is evidence they were followed;
- Whether the vendors/CRO train all study team members and if there is documentation filed in the TMF for this;
- Whether oversight was conducted and evidence that the internal study team knows its responsibilities;
- Documentation of changes and deviations that can be traced, linked to data and supported by reasonable proof of resolution; and
- Compliance with regulatory requirements for reporting.

Electronic trial master file (eTMF) systems can help with the task. They can flag documents that aren't finalized — documents that may still be in progress, rejected by quality control or awaiting quality control review. This assessment is helpful for rounding up documents still in need of approval.

Clues can also be drawn from previous completeness and inspection readiness reviews, Wiggins said. Go through past assessments (which should be documented in the TMF to show proof of oversight) with an eye for queries and whether they were answered. While this can help identify queries that may be blowing in the wind, it may also identify a lot of work to be done, she cautions. But doing this can bring different functional groups into the mix that may have competing priorities and different perceptions of the TMF's importance.

"You might need to assess what queries are of highest importance to review and close based on your timelines and available resources. We all know it's hard: there's time constraints and resource constraints, so sometimes you're going to have to triage those queries," she said. "In doing so, you can help engage functional groups with a clear and common goal."

Getting different functional groups involved and identifying the people within them who can help contribute toward TMF inspection readiness is also critical. Overall, departments should fully understand how their content is linked to inspection readiness. Missing CVs or training files from one group, for example, means that the TMF is incomplete. Help all groups understand their obligations and risks and offer support on managing them, Wiggins says.

"You want to bring functional groups together for a common goal of understanding the story of the study and find champions within each department who can help drive change," she said.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
Alterity Therapeutics	ATH434	Multiple system atrophy	IND approved by the FDA
Artiva Biotherapeutics	AB-201	HER2-expressing cancer	IND approved by the FDA
Immunitas Therapeutics	IMT-009	Solid tumors and hematological malignancies	IND approved by the FDA
Verismo Therapeutics	SynKIR-110	Mesothelin-expressing ovarian cancer, cholangiocarcinoma and mesothelioma	IND approved by the FDA
Xpira Pharmaceuticals	Psilocybin	Anorexia nervosa	IND approved by the FDA
Belite Bio	LBS-008	Stargardt disease	Approval for a phase 3 trial granted by China's regulatory authority
Psyence	Psilocybin	Adjustment disorder due to an incurable cancer diagnosis	Approval for a phase 2a trial granted by the UK regulatory authority
Trials Initiated			
Mind Medicine	MDMA-like substances	Mood disorders	Initiation of phase 1 trial
RVAC Medicines	RVM-V001 vaccine	COVID-19	Initiation of phase 1 trial
Revolution Medicines	RMC-6291	Cancers driven by the KRASG12C mutation	Initiation of phase 1 trial

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Drug & Device Pipeline News

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Company	Drug/Device	Medical Condition	Status
Amydis Diagnostics	AMDXP-2011P	Parkinson's disease and amyotrophic lateral sclerosis	Initiation of phase 1/2 trial
Immunis Biomedical	IMM01-STEM	Muscle atrophy	Initiation of phase 1/2 trial
Glyscend Therapeutics	GLY-200	Type 2 diabetes	Initiation of phase 2 trial
Vir Biotechnology	VIR-2218 and VIR-3434	Chronic hepatitis D virus	Initiation of phase 2 trial
Genelux	Olvimulogene nanivacirepvec	Platinum-resistant/refractory ovarian cancer	Initiation of phase 3 trial
POP Biotechnologies	EuCorVac-19 vaccine	COVID-19	Initiation of phase 3 trial
Approvals			
Bluebird Bio	Skysona (elivaldogene autotemcel)	Cerebral adrenoleukodystrophy	Approved by the FDA
Biocodex	Diacomit (stiripentol)	Seizures associated with Dravet syndrome	Approved by the FDA for expanded age indication
Eli Lilly	Retevmo (selpercatinib)	Advanced or metastatic solid tumors with an RET gene fusion	Approved by the FDA
Heron Therapeutics	Aponvie (aprepitant)	Postoperative nausea and vomiting	Approved by the FDA
Marius Pharmaceuticals	Kyzatrex (testosterone undecanoate)	Hypogonadism	Approved by the FDA
Edwards Lifesciences	PASCAL Precision transcatheter valve repair system	Degenerative mitral regurgitation	Approved by the FDA
AstraZeneca	Lynparza (olaparib)	HRD-positive ovarian cancer	Approved in China
Merck			

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