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Innovating for the Future of Drug Development

Contents

The Future of Drug Development is Now

The future of clinical trials has never been in more need of innovation to keep advancing against patient needs. Advances in technology, scientific discovery, data processing, and ways of engaging patients are moving clinical research to the bleeding edge. And with R&D investments by sponsors continuing to escalate, with one estimate putting expenditures at $233 billion in 2026 up from $186 billion in 2019, innovative thinking by leaders spanning the drug development journey are needed to bring new breakthrough medicines to market to meet a multitude of unmet therapeutic need.

Within this eBook, Parexel subject matter experts speak to some of the exciting trends that are moving the industry toward the drug development of the future, including the next era of precision medicine based on identifying tumor agnostic therapies, linking real world data to connect the dots for improved therapeutic outcomes, using synthetic control arms to link patients across multiple datasets using RWE, engaging patients in new ways to participate in virtual or decentralized trials, and addressing the very specific needs of patients and caregivers in the realm of rare diseases. The common theme throughout this publication is a dedication to innovation and moving the needle of drug development and clinical trials forward and a future where patients are at the heart of the process.

Embarking on the Next Era of Precision Medicine

Angela Qu, M.D., Ph.D.
Vice President, Biomarkers and Genomic Medicine, Translational Medicine, Parexel

Angela is an innovative subject matter expert and team leader in Genomic Medicine and Clinical Research. She has 20 years of experience working in pharmaceutical R&D and CRO clinical development. At Parexel, she leads therapeutic strategy development and implementation of genomics and biomarker studies, provision of scientific guidance, and consulting on partnerships with sponsors across broad therapeutic areas with a focus in Oncology and Immuno-oncology. She is a core member of Parexel's Oncology CoE (Centre of Excellence) and serves on multiple oncology professional committees.

The American Society of Clinical Oncology defines tumor-agnostic therapy as a type of therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. It is a type of targeted therapy. Also called tissue-agnostic therapy.

"This is an expansion from the current precision medicine model that primarily targets one tumor type guided by a biomarker," explains Angela Qu, M.D., Ph.D., Vice President, Biomarkers and Genomic Medicine, Translational Medicine, Parexel. "Moving into and across multiple tumor types, a so-called pan-cancer drug development approach guided by multiple biomarkers, is a game changer. This is a dream field for both drug developers and patients."

Patients with multiple tumor types are already seeing the benefits as evidenced by the four pan-cancer drug approvals in the past four years. In May 2017, the FDA approved Merk's Keytruda, a PD-1 inhibitor pembrolizumab, which became the first drug to receive tumor-agnostic approval in oncology — a watershed in the history of precision medicine. Keytruda received a second approval in in June 2020 to include any cancer with a high tumor mutational burden (TMB-H). Experts credit Keytruda's approval as revolutionary not because of the mechanism of action, but because the FDA approved it for the treatment for any unresectable or metastatic solid tumor with microsatellite instability-high or mismatch repair deficient biomarkers. In essence, the FDA approved the biomarker as the indication rather than approving the drug for a particular tumor type. For the first time ever, as long as a tumor has the biomarker, it doesn't matter where it is in the body; Keytruda may be considered to treat it.

In 2018, U.S. regulators approved Bayer's Vitrakvi (larotrectinib) for NTRK gene fusion tumors. In 2019, the FDA approved Roche's Rozlytrek (entrectinib), a treatment for adult and adolescent patients whose cancers have the specific genetic defect, NTRK (neurotrophic tyrosine receptor kinase) gene fusion, and for whom there are no effective treatments. At least 10 additional tumor-agnostic therapies are in development, based on a range of genetic mutations, including mutations in the RET gene, found in 2.21% of all cancers, and mutations in the neuregulin 1 gene (NRG1), which is found across solid tumors in lung, pancreas, and breast tissue. [Cancer World]

With cancer being the second leading cause of death in the United States, preceded only by heart disease, and estimates suggesting that almost 40% of Americans will be diagnosed with cancer at some point in their lives, there is a real need for new research innovation. While tumor-agnostic patient inclusion in clinical trials is not a novel concept, what is new is the ability to enroll molecularly enriched patients as part of basket trials for cancers that have one or more molecular alterations, where these alterations have a reasonable likelihood of predicting response to a particular therapy based on preclinical functional

The global liquid biopsy market size is expected to reach $ 5.96 billion by 2030, exhibiting a CAGR of 13.4% during the forecast period. Enhanced view of tumor provided by liquid biopsy technology is estimated to augment the market in coming years.

Source: Grand View Research, Inc.

and/or computational modeling, and these alterations are found across a variety of cancers. Angela is excited by the prospects of taking a transformative approach to developing precision medicines based on tumor-agnostic trial designs, which can be conducted in different ways but under an overarching master protocol, often with specific treatment arms or baskets for cancers of different origins. Another new type of trial, an umbrella trial, studies multiple therapies in different biomarker-matched patient subgroups with the same cancer histology.

One of the innovations needed to develop tumor-agnostic drugs are clinical trials that are designed to span multiple histologies, which is made possible by an increased scientific understanding of disease mechanisms. "Advances, from a drug development perspective, are also being driven by scientists and medical researchers who are able to dive deeper into the data and leverage genomic technology to understand the link between the underlying disease and the association with the tumor types or other disease conditions."

Angela credits regulatory bodies, which have made significant strides in supporting and advancing precision medicine and genomic biomarker development, for applying scientific rigor to come to a greater understanding of the demonstrated efficacy and safety of these new therapies that meet such huge unmet medical needs. Angela was honored to provide feedback as an invited panelist on a recent U.S. Food and Drug Administration and American Association of Clinical Research initiative on a precision medicine melanoma drug development program. "We should be working together from a regulatory and an industry perspective to navigate this cutting-edge space," she says.

Parexel is well-positioned to lead the transformation in this area, as Angela notes the company has deep subject matter expertise in regulatory, technology, data, and clinical trial innovation. "We have designated teams in all of the innovation areas, ranging from translational medicine, which allows us to establish the connectivity between genomic/biomarker data to identify the targeted patients, to teams that are experts in adaptive trial design and modeling/simulation innovation, to determining the right dosing and improving trial efficiency," she says.

If the ultimate goal for precision medicine is to get the targeted therapy to the right patient

Cancer biomarkers are molecules or specific processes that signal the presence of cancer. Biomarkers can be proteins, genes or gene mutations, molecular modifications, or microenvironmental changes. Generally, biomarkers are disease or process specific. For example, breast cancer biomarkers allow sub-typing based on hormone receptor status (e.g., estrogen-receptor positive, HER2-positive, and triple negative). In lung cancer, various mutations such as EGFR, ALK, ROS-1, and BRAF are biomarkers used to subtype non-small cell lung cancer (NSCLC).

population, then determining the right dosing is one of the keys to success. Not all patients can take the same dosage of the same drug and receive the same benefits. From a trial design perspective, dosing based on genetic or genomic make up should be factored in so as to account for the variance in how patients process different drugs. "A drug that may be beneficial to you might be toxic to me because the dose is too high as I may carry a genetic variation," Angela says.

While initial success has been in the area of oncology, Angela says other areas such as rare disease, could benefit from the advances being made in precision medicine. There are more than 7,000 distinct types of rare and genetic diseases impacting more than 400 million people globally. And eight out of 10 of these diseases are caused by a faulty gene.

"We are already seeing an uptake from FDA in regard to the drug approvals from precision medicine in rare disease areas, including the spinal muscular atrophy for example and Duchenne's muscular dystrophy," she says.

Another area of innovation that excites Angela is the field of liquid biopsy. Liquid biopsies, unlike tissue biopsies, which despite their highly invasive nature have been the standard for cancer diagnosis for several years, offer a less invasive methodology along with high effectiveness.

"We can use this noninvasive approach for genomic biomarker interrogation, which allows for patient selection from a diagnostic perspective and give us the ability to dynamically monitor the treatment response during a clinical trial," Angela says.

Angela is optimistic about the future and the role that Parexel will play in advancing precision medicine, even expanding beyond high throughput genomic technologies and big data generation into the next generation of omics, which she has coined as "clinico-omics." "This is clinical data plus genomics plus real-world data or real-world evidence," she says. "And, 'patho-omics' — digital pathology plus genomics data. At Parexel, we are pioneers in this space; we are developing and refining genomic and biomarker strategies, applications, and innovative approaches to help us generate insights in the precision medicine space. This is a very exciting time."

Precision medicine leverages one or more biomarkers, often genetic or genomic in nature, to guide therapy decisions. A biomarker is a defined and measurable characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions. The biomarkers are indicators of how the drug will be metabolized in the body, who is most likely to benefit, or who may be at risk of side effects.

Source: Parexel

Connecting the Data Dots

Jennifer Hebert
Senior Director, Global Head of Scientific Data Solutions, Parexel

Jennifer brings more than 15 years of experience in worldwide clinical research, program leadership and solutions development. She has expertise spanning RWD/scientific data solutions architecture to data driven monitoring, data surveillance, data management, clinical monitoring, and project management. She has operational level experience in EDC database development, data processing, coding, SAS programming, integration of systems and external data, SOP development and adherence, and resource training. She has rich experience implementing innovative solutions and new methodologies in clinical research.

Drugs developed using RWD in Phase II and III have a 21% greater likelihood of launch across all therapeutic areas, this is according to a 2018 report, The Innovation Imperative: The Future of Drug Development from the Economist Intelligence Unit (EIU), commissioned by Parexel.

So, it's no surprise that "emerging use cases" of real-world data (RWD) are part of Parexel's focus on innovating for the future of drug of development. Integrating RWD, stemming from a variety of sources, including clinical data repositories, commercial data sources, EHR systems, wearable and sensor data, into one data platform creates more robust and richer insights to support a therapy's safety or efficacy assessment. Indeed, real-world evidence (RWE) can help in developing hypotheses for testing in randomized controlled trials (RCTs), in identifying potential biomarkers, assessing trial feasibility, as well as long-term patient insights.

The challenge is linking together the disparate data sets into one platform while overcoming data standardization, operability, patient linkage challenges, and also meeting regulatory standards around the world. In support of RWD, legislators, policy makers, and government agencies are increasingly looking to RWE to support regulatory or market-access decisions — a critical step forward in the industry's ability to apply an understanding of real-world patient care and outcomes to the drug approval process.

Jennifer Hebert, Senior Director, Global Head of Scientific Data Solutions, Parexel, and her team are working to unlock the promise of what this data can bring and overcome the barriers to using RWD by exploring new ways of creating meaningful data links.

The data that holds the most value is generally multi-model data; data that is capable of surfacing the deep and meaningful insights that sponsors are looking for beyond what's available from the clinical trial data alone," Jennifer says. "We want to unlock data that will tell us more about each individual patient over a longer time period, which can highlight the benefits of personalized medicine and be truly patient-centric. But in order to do that, we need a way to link all the data

together while protecting patient privacy. This will give us the whole picture of how patients are interacting with the health system, the pharmacy, personal devices — all of the real-world data sources that are available."

Her goal is to have a platform that can collect and bring all of the data together, link it, and then provide it back in such a way that study teams can integrate the information and tap into an analytic dashboard to see the data in near real time.

"This approach will allow us to track the quality and quantity of data that's coming in to see if it's sufficient for analysis," Jennifer says. "This convergence of streaming data unlocks patient journeys and outcomes, which allows us to process clinical insights that otherwise would be hidden until the end — this is the innovation."

Case in point, if a patient is tokenized during enrollment in a Phase 2-3 trial for example, then that patient's data can be seamlessly transitioned to observational extension studies, which can then be linked to real world data sets to support market access or medical-affairs analyses. "This process can reduce the recruiting time and the cost for later studies," she says. "And, ideally fewer patients would be lost to follow up because through real-world data we can monitor them. This is not just about claims, we can increasingly access EMR, socioeconomic, and in some cases mortality data."

The first step of the process, however, is to plan ahead and encourage patients to consent to having their personal identifiers tokenized to protect their privacy. "This is critical as it allows us

Defining the Data

Technology advances at a breakneck speed, and there is an enormous variety of data types. A 2018 report, The Innovation Imperative: The Future of Drug Development from the Economist Intelligence Unit (EIU), commissioned by Parexel, offers useful definitions of the two:

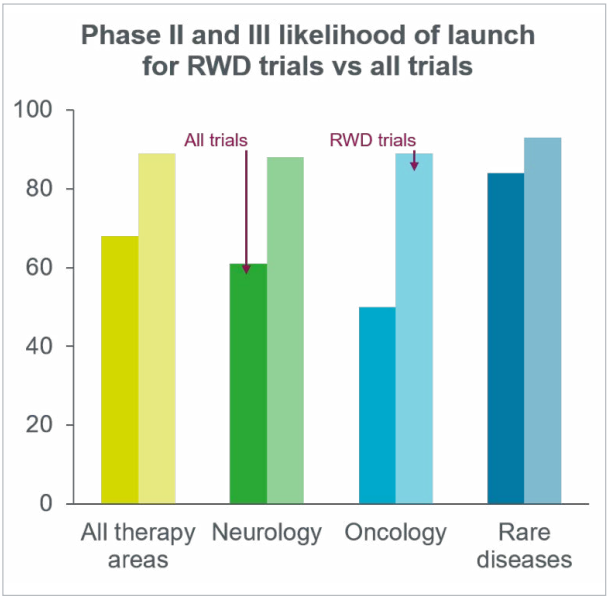
REAL-WORLD DATA

RWD is data collected from various sources outside a typical clinical research setting, such as a randomized clinical trial (RCT). Essentially, these data are a by-product of the patient's experience during their journey through the disease. Data can include electronic health records, pharmacy or payer claims data, product and disease registries, observational studies and patient-reported outcomes, as well as data gathered through personal devices and health applications, such as social media and wearables.

REAL-WORLD EVIDENCE

RWE is generated according to an analytical plan and interpreted accordingly, essentially transforming the data into meaningful evidence. This data can be used to generate insights about a product's effectiveness.

later on or even at that time, to look for overlaps within commercial or other data sources," Jennifer says. "This is what allows us to unlock all of the data and provide the linkage."



Facilitating data sharing across payers, the public sector, and provider organizations, will empower patients. Patients will be able to assume better ownership around decisions relating to their care. "But for the purposes of bringing data together to support analysis we need more than that," Jennifer says. "This is why we are pulling together all of the different pieces and creating a data link that includes tokenized patient data for analysis by using analytics, AI, and algorithms."

Jennifer notes ultimately to be successful an important part of her mission is to help educate patients on how the technologies work and how the process serves to protect them and their privacy. "We need to explain why patient participation in the clinical trial process is a gift that enables future research and long-term follow up," she says.

Entering a New Age of Evidence Generation: Synthetic Control Models

Leanne Larson
Senior Vice President and WW Head,
Real-World Evidence & Access, Parexel

Leanne Larson brings more than 25 years of experience in healthcare, featuring extensive work in pharmaceutical product development and commercialization, and in healthcare technology and operational consulting. Leanne is an industry leader in designing and leading observational / non-interventional studies and in advancing the science of outcomes research, and publishes and speaks widely on a variety of topics in this area. Before joining Parexel, Leanne served as VP for Quintiles/ Outcome, ICON, and Sg2 Healthcare Intelligence.

The industry is primed to take real-world evidence (RWE) to a whole new level through the use of external data to create synthetic controls for clinical evaluations. Some say this shift might be

considered radical, but for others such as Leanne Larson, Senior Vice President and WW Head, Real-World Evidence & Access at Parexel, she and her team are ready to meet the growing interest in RWE from sponsors, regulators, and payors, by developing innovative data models and technologies, to transform clinical research.

A Summary of Commonly Used Models and Methods for Generating Synthetic Control Arms

MODEL COMPLEXITY	EXAMPLES	PROS	CONS
Naïve	Simple mean, median or fixed-effect pooling	Easy to perform. Easy to interpret.	Requires high congruence between external and internal data. Often only valid for restrictively small sub-group populations. Thus, falls short on precision.
Imbalance Adjustments	Multivariate regression, propensity scoring	Adjusts for imbalance to the extent explanatory factors are available in data. Relatively easy to perform. Relatively easy to interpret. Generally considered valid with good data and sufficient plausible confounding variables.	Methods can be complex or relatively time consuming to implement and test. There is a plethora of approaches with various performance advantages and shortcomings. Thus it may be challenging to choose the "best" approach. Examples of applications with counter-intuitive findings exists, thus underscoring the need to have available and consider as many possible confounders as possible
Complex adjustment and weighting	Bayesian mixed-model commensurate power priors.	Can restore patient balance and weigh the contribution of multiple sources of data adequately.	Difficult and complex to implement. Often computationally heavy.
Advanced exploratory solutions	Random forests, Neural Networks, Cluster analysis (Gaussian mixture models)	Can identify homogeneous sources of data for enhanced validity.	Mostly exploratory in nature and requires separate statistical analysis to produce synthetic control. No guarantee findings will be interpretable or useful for further analysis.

Source: National Center for Biotechnology Information, U.S. National Library of Medicine

Synthetic control models, which are not new to clinical research, can be used to evaluate the comparative effectiveness of an intervention using external control data. What is revolutionary though, is the opportunity to use existing data and to link patients across multiple datasets, in concert with proven prospective research models within non-traditional infrastructure settings. According to Leanne, this approach offers important opportunities both to streamline the research process and to bring needed real-world perspective and data to the table. "We have greater access to better data than we did a number of years ago, so our ability to gather the data that we need for the synthetic control arm has significantly improved — and without these advancements, synthetic modelling at this level would never be possible," she says.

Real-world data also can provide important information in the post-marketing setting, especially from a safety perspective, to answer both regulatory and payor questions. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have taken several initiatives to allow for these novel approaches to external control data.

In a review of 489 pharmaceutical technologies assessed by the National Institute for Health and Care Excellence (NICE), according to the National Center for Biotechnology Information, US National Library of Medicine, as of May 2020, 22 submissions used external data and synthetic control methods to establish clinical efficacy. Of these, 13 (59%) used published RCT data for

While the concept of synthetic control arms may be new to many, they have already been successfully used in regulatory decision-making. Roche, for example, met European Union coverage requirements for marketing Alecensa (alectinib) in 20 European markets using a synthetic control arm. In December 2015, Alecensa received accelerated FDA approval as a treatment for a specific form of lung cancer, and in February 2017 it was conditionally approved in the EU. To make a pricing decision, EU authorities requested additional evidence of Alecensa's effectiveness relative to the standard of care (ceritinib). Rather than waiting for Phase 3 results, Roche used a synthetic control arm of 67 patients to provide the necessary evidence of relative performance. The decision to use a synthetic control arm advanced coverage of Alecensa by 18 months in 20 European countries. Another example is Amgen's use of a synthetic control arm to accelerate the approval of Blincyto (blinatumomab) for the treatment of a rare form of leukemia.

their external control, and six (27%) used observational data. More than half of the applications were made in the last two years alone, further confirming the increasing attention paid by both drug manufacturers and health technology assessment agencies on this topic.

These numbers support Leanne's read on the biotech and pharmaceutical industries' excitement around the potential of external controls, and their benefits in accelerating clinical timelines, reducing costs, and decreasing the number of patients required for clinical studies. "Today, we have a greater understanding of the robust statistical methodologies that are required, as well as an overarching comfort level and the experience in working with the real-world evidence that supports this new approach," Leanne says.

Even with all of the benefits, however, a synthetic-control model is not appropriate for every study, or every product. "Currently, we see the greatest potential in the areas of rare and life-threatening diseases, where finding study participants is particularly challenging," she says.

Patients, particularly those facing a complex illness, are often hesitant to enroll in a clinical trial where they run the risk of being randomized to either a placebo control or a control that they fear may be less effective. In this model, though, they are assured they are receiving the innovative, experimental treatment that they hope will offer some relief. "There are also some cases when it's not considered particularly ethical to enroll randomized patients in a placebo control, for instance," she says. "Patients need to be treated, especially in areas of unmet medical need, where there might not be an accepted or effective treatment for that condition."

Leanne and her team are at the forefront of this burgeoning area of research and are well-primed to assist sponsors to determine whether a synthetic-control arm is appropriate for their clinical protocol. Parexel's innovative and consultative approach, based on years of experience, starts with a tremendous amount of due diligence. "We have a well-structured model that we follow," she says. "Based upon our experience in this model, we have a list of questions that we ask, and we know what we need to consider in order to determine whether or not the sponsor's project is appropriate for this approach."

Her goal is to make sure at the outset that the correct study design is in place with the right covariates and endpoints, and that the external patient cohort is comparable to the patient population in the clinical trial treatment arm. "We want to ensure that the synthetic control population mimics the experimental population as closely as possible," Leanne says. "And, justifiably, in some cases the criteria that the agencies are utilizing are even more stringent than if we were conducting a randomized study. We want to ensure that we have the best, most-robust and most-representative dataset possible. We match the patients in the synthetic control arm to the patients in the experimental arm as closely as possible so that we can draw the right conclusions from the data."

With the growing need to achieve better value for healthcare, RWE as a decision-making tool is more important than ever as part of the drug development and commercialization process. Amid the various factors that contribute to costly trials and long development timelines, there is increasing recognition that through synthetic controls and other real-world approaches, it is possible to achieve a better understanding and stronger evidence of product performance, clinical value, and cost effectiveness outside the controlled environment and homogeneous setting of the randomized clinical trial - in the end, allowing us to better inform the healthcare decision-making process.

"As all of the stakeholders gain more and more experience with synthetic control arms, and as our data science and statistical approaches continue to evolve, we will see greater use of this very patient-centric model," Leanne says. "Not only does it help make the research process easier on patients, but it also helps us, hopefully, accelerate our ability to bring important new therapies to patients who in many cases don't have other effective treatment options."

Bringing Clinical Trials to Patients with the Decentralized Model

Rosamund Round
Vice President, Patient Innovation Center, Parexel

Rosamund is dedicated to improving clinical research access and experiences for patients and caregivers and is passionate about creating new and exciting ways to do so.

Before the pandemic, Parexel was experienced at executing decentralized clinical trials to improve patient access and experiences. Since, COVID-19, which has had a huge impact on global clinical trials, sponsors, CROs, sites, and patients have pivoted to adapt to a more home- or community-based approach. More than 100 DCTs later, Parexel is at the forefront of industry change.

"Everything we do is built around the patient and caregiver to make participation as easy as possible." says Rosamund Round, Vice President of Parexel's Patient Innovation Center. Central to navigating the dynamic research landscape is Parexel's ability to harness and apply patient insights during DCT planning to ensure that every part of the strategy is formulated

with the patient in mind. This approach, along with expertise in global regulatory requirements, technology implementation, and operational deployment, makes the company a leader in decentralized clinical trials.

Rosamund and her team address every aspect of the clinical trial experience keeping the patient's perspective top of mind — from financial considerations to geography. How far does a patient live from a site? Can the patient afford to take time off of work or afford the transportation? Are there childcare issues?

"These are the everyday life considerations that people think about when they join a trial, aside from purely the medical aspect," Rosamund says. "We talk to patients and caregivers from the start to ensure we truly understand what the biggest issues are for them and how we can help. The rest of the strategy is built from there. Working this way can also positively impact research access for those who may otherwise find it challenging to participate in research. And, with thoughtful and collaborative planning, a positive experience can also improve compliance and reduce dropout."

According to Rosamund, by bringing a trial to a patient's home – with the help of home healthcare support, telemedicine and sensors, direct-to-patient drug shipments, and more – she and her team are minimizing recruitment and retention barriers. "All of these elements, combined with the expertise of our Patient Innovation Center and best-in-breed technologies, are essential to creating DCTs that work for patients and can be practically deployed as part of a sponsor's overall clinical development and market access strategy."

DCTs & Digital Working Hand in Hand

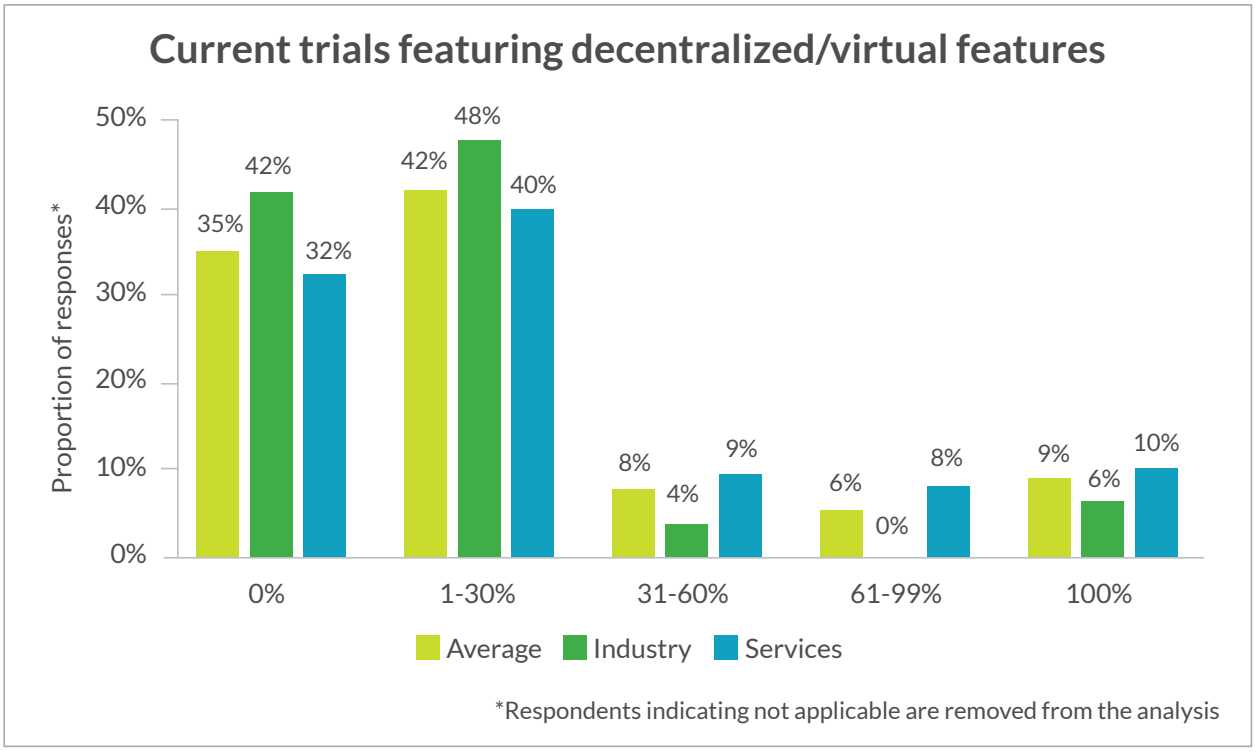
With sponsors sitting anywhere on the spectrum from being new to the world of DCTs through to adopting at scale, Parexel's DCT Consultancy service provides guidance and partnership for success. They are ready to advise on the following:

- Pipeline review for DCT target identification
- DCT study design
- Service identification e.g. home nursing, patient recruitment, technology solutions
- Budget planning
- Regulatory acceptance of DCT services
- Training
- Patient insights
- Pandemic risk mitigation

Rosamund and her team work through the minutiae of every element of the patient experience from start to finish, even down to which charger goes with what device. "In decentralized trials, it's important to consider the varying comfort levels of participants when it comes to technology and having healthcare staff in their home," she says. "We want to support patients and their caregivers to ensure they understand how the technology or wearable works, what happens when the home nurse comes to visit, and how to manage the delivery of their medications. If need be, through our Patient Navigator Service, they can speak to a real person on the end of the phone who can help them with anything they need, from simple things like organizing a taxi or rescheduling an appointment, support for their first home-based visit all the way through to counselling for the participant and caregiver if they are struggling with their mental health."

This intense attention to detail will no doubt come into play with increasing frequency as the industry continues to move toward a hybrid or fully decentralized model. A new report from the life-science data analytics company GlobalData has found that 67% of the 150 healthcare experts surveyed during the summer of 2020 plan to work in the DCT model. This is a direct result of COVID-19, during which many utilized home visits, medication deliveries, and telehealth, which was actively encouraged by the FDA and to ensure patient safety, trial continuity, and data quality of trials during the pandemic lockdown.

Through Parexel's discussions with physicians Rosamund says they have heard that, contrary to what many thought of telehealth pre-pandemic, have actually had a very positive experience. Compliance



Source: PharmaIntelligence Informa, July 2020

has increased due to reduced patient burden, real human connections have still been possible and they report having unique insights into patients' lives outside of the traditional site model.

"My vision is that patients have choices so that research participation is as easy as we can possibly make it for them," she says. "In recent months, people have seen what's possible and we need to meet their expectations in the long term beyond the pandemic to enable clinical trial access for those who need it the most."

Rosamund is confident that whatever challenges the world may throw at them — now, and in the future — Parexel's Decentralized Clinical Trials represent an opportunity to rethink and refresh how research studies are conducted, while keeping the patient at the heart of this exciting paradigm.

Making Rare Disease Drug Development Personal

Sarah Glass, Ph.D.
Global Head of Rare Diseases, Parexel

Sarah is a geneticist and drug development professional with demonstrated success in precision medicine and rare disease drug discovery and development. She has an exemplary track record in leading matrix teams to deliver customized clinical development strategies that encompass scientific and medical rigor, patient-centricity and operational efficiencies.

Shipra Patel, M.D.
Global Head of Pediatrics, Parexel

Shipra is a board-certified pediatrician and pediatric endocrinologist. As a Global Head of Pediatrics at Parexel, she has gained extensive experience through medical monitoring for several type 1 and type 2 diabetes trials, as well as pediatric trials. She is leading the pediatric working group at Parexel and is focused on optimizing clinical trials for pediatric patients with rare diseases.

The statistics regarding rare diseases speak for themselves: one of two patients diagnosed with a rare disease is a child; three of 10 children with a rare disease won't live to see their fifth birthday; more than 400 million people suffer from a rare disease globally — greater than the population of the U.S. Fortunately, the drug development landscape for rare diseases is increasing exponentially. However, there are many challenges in conducting rare disease clinical

trials, including small populations often spread across the globe, limited opportunities for study participation and replication of results in larger trials, and heterogeneous manifestations of disease and phenotypic presentations. The clinical manifestations are often not easily connected to a specific disease — on average, a rare disease patient visits seven specialists, and a correct diagnosis can take as long as six to eight years — and a lack of consensus on clinical outcome measures and poorly defined endpoints.

Sarah Glass, Ph.D., Global Head of Rare Diseases, Parexel, and Shipra Patel, M.D., Global Head of Pediatrics at Parexel, strive to overcome these challenges on a daily basis. The development of a comprehensive customized clinical trial solution that incorporates a sound clinical, scientific, regulatory, and market access strategy allows their Rare Disease and Pediatric teams to overcome these challenges. Most importantly, a deep understanding of the patient and caregiver journey is at the center of every successful clinical development program. As the number of effective treatments for rare diseases grows, the industry will continue to adapt to changing clinical trial models, regulations, technologies, and reimbursement landscapes to meet the needs of rare disease patients.

THESE FACTS SHOW THE IMPACT OF RARE DISEASE

1 in 10
People are Affected by Rare Disease

1 in 2
Rare Diseases Don't Have a Foundation or Research Support Group

1 in 2
Patients Diagnosed with a Rare Disease is a Child

3 in 10
Children with a Rare Disease Won't Live to See Their 5th Birthday

400
Million People Suffer From a Rare Disease Globally (greater than the population of the U.S.)

8 in 10
Rare Diseases are Caused by a Faulty Gene

6-8 Years
Average Time to Get an Accurate Rare Diagnosis

95%
of Rare Diseases Lack an FDA Approved Treatment

RARE
Diseases Impact More People Than Cancer and AIDS Combined

7000
Distinct Types of Rare and Genetic Diseases

Source: Global Genes

"We are looking at how to make the trial process easier for the patients and families," Shipra says. "We look to see how we could make some of the assessments work in a decentralized clinical trial setting. Is it possible to do some evaluations at home? Is it possible to reduce the time spent at the site while still preserving the quality of the trial? These are just a few of the questions we ask ourselves all of the time."

"In addition to a focus on decreasing patient and caregiver burden in a clinical trial setting, Parexel ensures data is embedded to drive decisions throughout the clinical trial and development program," Sarah says. "This data may include natural history data as comparator arms, pharmacokinetic /pharmacodynamic data to understand mechanism of action, or biomarker and genomic data to understand drug response."

Parexel is embarking on a new era of rare disease and pediatric drug development, founded upon:

- **Precision medicine concepts** — every population is unique and we leverage medical and scientific expertise to treat every rare disease program using a precision medicine approach through enhanced understanding of the patient characteristics and applications to drug development.
- **Protecting the endpoints** — data integrity is at the core of a successful clinical trial and it is critical to ensure the delivery teams have this enhanced appreciation and relevant training.
- **Embedding patient insights** — Not seeking input only but translating patient input into actions.
- **Optimizing trial design to focus on the needs of children and their families** — to shorten trials, increase efficiencies, and leverage real-world data / natural history studies.
- **Hybrid trials** — optimizing every protocol and clinical trial design by ensuring patient-centric sampling and schedule of assessments, and exploring the possibility for decentralized or home-based options for some visits and assessments when it is appropriate in each indication.
- **Patient support services** — Providing travel, childcare, lodging, patient, and family concierge services as the disease pathway and patient necessitates.

Sarah says Parexel is innovating to address these goals by understanding the whole patient journey. "We strive to seamlessly align the clinical trial solution with the patient journey, which often starts many years prior to diagnosis," she says. "It is our obligation to understand the patient journey, including specialty care, referral pathways, and support groups to ensure that every patient is aware and if their indication warrants, given the opportunity to participate in a clinical trial if he or she chooses to do so."

Beyond mapping the patient journey, the Parexel team is also helping to pave the path of what happens outside of the clinical trial through knowledge sharing, working with sponsors, and providing support.

"Awareness campaigns are often an important component of patient identification and recruitment efforts to make sure that the physicians or the people who are going to interact with those patients and those families at the earliest part of their journey are aware of a particular study and why a study might be beneficial to that patient population," Sarah adds. "We strive to ensure broad and effective knowledge-sharing regarding a clinical study, to ensure patients and caregivers can make timely decisions regarding clinical trial participation, which can have a meaningful impact on their disease prognosis."

Shipra adds this is why it's so important to know the standard of care for these diseases by working with and having relationships with key opinion leaders in the rare disease space. In this way, she notes, she and her team have a better sense as to the point at which they can recruit patients and the best way to do so.

"Engagement with key opinion leaders is critically important because they already have experience in the disease space," she says. "These KOLs are often field-leading medical experts in rare disease who have intimate knowledge of the disease and they know the patients and their families by name. These investigators are key to recruiting pediatric patients given the trust each patient and caregiver has in them."

Shipra and Sarah highlight the importance of rare disease and pediatric clinical trial solutions that address not only the needs of the patient but also the entire family unit. "Our Patient Innovation Center is a dedicated group focused solely on embedding components that will decrease the burden and optimize the clinical trial experience," Sarah says. "This is especially critical in many rare diseases when the treatment under investigation is the only hope these families have." These components may include transportation and lodging, child care, or facilitating specialty visits, so that families can also continue with other aspects of their lives outside of the clinical trial.

"While collectively rare diseases affect hundreds of millions of individuals worldwide, the reality is that every single individual affected by a rare disease is precious and unique," Sarah says. "For us at Parexel, this means that even within an indication where the clinical trial landscape is robust, we must customize that trial solution based on the specific characteristics of those amenable to treatment with that drug. We embed patient insights into our broader trial solution and strategy, as well as into indication-specific clinical trial solutions. Part of our remit is to ensure that we are embedded in the rare disease community and not operating in isolation. We are in a unique and advantageous position to be a neutral party between the patients/ families/ physicians and the sponsors are able to embed key scientific and medical knowledge as well as patient perspectives across clinical trials in an unbiased manner."

Every clinical trial solution developed and run by Parexel is done with the intent to support a sponsor through to drug approval. This ensures the highest level of data integrity and ability to

be audit-ready. "At Parexel, not only have we contributed to more than 15 rare disease drug approvals, but we also have dozens of former regulators as part of our organization," Shipra says. "Early insights from former regulators in a rare disease program can put the sponsor one step ahead and mitigate significant risk for delays. This is also important in having regulatory buy in for the endpoints to be used for trial registration."

"Every patient, every data point, every sample is precious and unique," Sarah says. "Because we have the privilege to develop these clinical trial solutions for the rare and pediatric populations, it is our obligation to ensure every aspect of the clinical trial solution is developed with someone in our mind who we know and love and ensure that the solution would be suitable for them."

It is with that mission in mind that Sarah and Shipra at Parexel strive to accelerate the development of treatments for rare disease and pediatric patients, with heart.

The Partner of Tomorrow

The Parexel of tomorrow is based on fundamental principles that include putting patients first, quality, respect, empowerment and accountability. These principles have been at the heart of the company since its inception: getting medicines to those who need them.

By providing a comprehensive suite of biopharmaceutical services that help customers across the globe transform scientific discoveries into new treatments, Parexel is reimagining the clinical trial journey at every juncture to improve the world's health by putting patients at the heart of everything we do.

With Heart

We're always available
for a conversation

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