A Breath of Fresh Air: How Decentralized Trial Options are Changing Respiratory Research

Respiratory teams are witnessing a shift from research condensed around common or prevalent conditions — such as asthma or COPD — to an expanded focus on rare diseases or distinct subpopulations who are symptomatic despite existing standard of care. This change in direction poses different challenges and opportunities for sponsors working in this space. Coupled with new obstacles brought to the surface by the COVID-19 pandemic, respiratory pipelines are increasingly acknowledging the importance of innovation, adaptation, and flexibility in clinical research. This has resulted in more sponsors embracing decentralized trial models and technology to facilitate some or all aspects of trial execution.

Tim Rich, Jenna McDonnell, and Wesley Hicks, PPD

In recent years, the focus of respiratory development has realigned to nurture lesser known indications with unmet needs. Examples of these rare diseases include progressive fibrotic interstitial lung diseases (PF-ILD), pulmonary arterial hypertension (PAH), cystic fibrosis (CF), and non-cystic fibrosis bronchiectasis (NCFB). Within more prevalent conditions, such as asthma and COPD, sponsors are increasingly focused on smaller subpopulations of patients who have a specific clinical or biomarker phenotype or whose disease burden remains high despite available therapy. Using biomarkers can aid the drug development process by reducing the time needed to bring a product to market.

Respiratory studies have an additional layer of complexity in that they do not typically involve healthy volunteers. In these cases, study populations may include patients with various levels of disease burden — even those with severe situations, such as end-stage respiratory failure. Therefore, in a traditional respiratory clinical trial model, accessibility is typically low while patient burden is very high.

The combination of studying smaller subpopulations, varying levels of disease complications, and increased patient burden has resulted in the need for a more flexible protocols utilizing digital and decentralized options to improve the accessibility of clinical trials for all, ultimately bringing the study directly to the patient.

The Journey to Decentralized Clinical Trials (DCTs)

In the years leading up to the COVID-19 pandemic, PPD made strategic investments together with the creation of a specialized unit known as PPD® Digital. This Center of Excellence (CoE) specializes in digital and decentralized trial design and technology. The team comprises a variety of experts who contribute to the operations, management, strategy, and design of DCTs.

Throughout this journey, we have helped sponsors transition from traditional clinical trial models into custom-fit decentralized solutions, using tools such as e-Consent, eCOA, telemedicine, and home healthcare visits with respiratory nurses to achieve acceptable endpoints with real-time data.

While there was increasing focus on how decentralization could be applied before the COVID-19 pandemic, many sponsors remained cautious or reluctant to apply these innovations. Historically, this is because DCTs have been perceived as difficult to operationalize and involved further consideration from leading regulatory bodies. However, the pandemic shifted the conversation from decentralization as an option to consider to an essential solution, creating a pivotal moment for the industry as a whole. PPD Digital has seen firsthand the transformation from using these solutions as an application to "rescue" ongoing trials into a tailored and proactive application of innovations for planned trials. This trend will continue to accelerate as the range of providers and solutions expands, and as the industry now has the experience and confidence to see these innovations as tried and tested solutions.

Special Considerations for Respiratory Clinical Trials

Adaptability must be built into clinical studies to provide the needed flexibility for patients who exhibit different needs, particularly those whose respiratory diseases are unpredictable and whose treatment requirements are just as complex. Technology must be woven into the layers of the human element involved.

As an example, clinical trials in asthma increasingly focus on rarer subpopulations with more complex drug

How do digital and decentralized solutions pair with respiratory indications?

Digital Solution	Description	Respiratory Research Application
eConsent	A fit-for-purpose tool to capture digital signatures on consent forms.	Enables stronger, more detailed communication between clinicians and patients, thereby increasing enrollment and recruitment.
Televisits	A visual communication tool used to facilitate investigator and patient engagement.	Those who might otherwise have problems stemming from physical exertion or exposure to outdoor elements can be conveniently seen by medical professionals — whether in person or virtually.
Home Healthcare	Qualified nurse to visit patients' homes and perform study assessments.	
Devices and Wearables	Collect real-time data and biometrics from patients anywhere.	Bluetooth-enabled handheld or portable devices, such as spirometers, inhalers, actigraphy, step counters, and fractional exhaled nitric oxide (FenNO) monitors, linked to a patient's smartphone or device. The modern options available for patients can also allow real-time data collection and monitoring by study teams.
eCOA/eDiary	Electronic clinical outcomes assessments and diaries for electronic collection of data	Reduces the need for patients with chronic or severe disease burden to travel to a site for a routine visit.

administration and thus face unique challenges, such as higher screen failure rates and fewer patients living close to the site. In addition, these patients are typically working age and often have career responsibilities, so frequent on-site assessments for investigational product (IP) administration or spirometry may not be compatible with their lifestyle. Decentralized strategies can help overcome many of these issues.

Special considerations for the execution of decentralized respiratory clinical trials include standardizing rater training, diagnostic criteria, mobile spirometry, and outcome measurements.

Spirometry vs. Remote Spirometry

Spirometry has traditionally been done at sites with centralized equipment and direct observation by site staff. This model ensures confidence in data quality but is less patient-centric, in that it requires patients to make frequent visits to a site. For many visits, spirometry is the sole driver behind the need for an onsite evaluation. While handheld 3G-enabled tools to collect peak expiratory flow (PEF) have long been applied in asthma trials, allowing real-time daily PEF capture, tools capable of collecting forced expiration (FEV1) and forced vital capacity (FVC) data at home have been limited until now. This transition from performing spirometry in the clinic to in the home is one of the last milestones in the decentralization of the respiratory clinical trial space.

Adaptability must be built into clinical studies to provide the needed flexibility for patients who exhibit different needs, particularly those whose respiratory diseases are unpredictable and whose treatment requirements are just as complex.

Options include:

Selection of site spirometer with portable capability for supervised use in patient's home

Patient handheld devices for home use with real-time remote supervision and coaching of maneuver by site staff via video link

Patient handheld devices with pre-programmed feedback loops, with subsequent central overread

In addition to these remote solutions allowing a reduction in onsite visits, they also allow sponsors to collect more frequent spirometry assessments, with the potential reduce variability in the data.

Actigraphy: Real-Time Data from Wearables

Another modern tool showing increased use in respiratory research is wearable technology. For example, a sensor unit that looks and feels like a wristwatch can enable actigraphy, a non-invasive method of monitoring human rest and activity cycles. This allows for gross motor activity to be measured in real time, along with other data, such as light exposure. These data are transmitted to clinicians and study teams to objectively measure patient functional status in their environment in a manner that was not previously possible. These are arguably more relevant and timely endpoints than others collected via traditional modes. In respiratory trials, these sensors would aid in the detection and classification of minimal clinically important differences (MCIDs) as patients are increasingly tasked with reporting their data remotely.

Monitoring Medication Use and Remote Adherence

The impact of adherence on patient outcomes has long been recognized in respiratory trials, but to date most studies still have only limited data sets. This includes patients using diaries to self-report the number of inhalations they have taken or to confirm that they have taken study medication. For some, rescue medication recall may be poor, and there is no understanding or visibility of when the patient is using the therapy. This has left many sponsors wondering if they can do more to increase visibility into medication use by participants.

Understanding adherence and use would enable earlier intervention to remind patients to comply with study dosing schedules or to detect patients relying on increasing amounts of rescue medication and flag those patients who need immediate clinical assessment. Automated, 3G-enabled smart pill containers not only can remind patients to take their medication but can also record and transmit time- and date-stamped confirmation of when pills were accessed. This real-time data transfer to the site allows earlier contact with patients to understand the reasons behind any non-adherence while providing retraining as necessary.

In a similar manner, inhalers leverage sensors to enable data collection for inhaled therapies. Digitally equipped inhaler use in clinical trials is on the

rise, with several solutions having been recently approved by the FDA. Most sponsors, especially those in earlier development, select Bluetooth-enabled devices that are complementary to the inhaler. However, the approval of Teva's Digihaler®, where the Bluetooth-enabled sensor is integrated with the inhaler at the time of manufacture, demonstrates that integrated solutions are possible and forthcoming. In both of these cases, data are automatically sent to site staff via a mobile app that the clinician can review to understand the patient's level of control, thereby forming a crucial part of a remote visit.

6MWT: The Six-Minute Walk Test

The 6MWT is a well-established test frequently used in trials of pulmonary arterial hypertension (PAH) and interstitial lung disease, and it can be predictive of mortality. It is used both as an eligibility criterion and as an outcome measure. Traditionally, the 6MWT has been required to be done onsite in a measured hallway and directly observed by a trained member of site staff. Challenges include the frequency of evaluations due to the requirement of rest periods between testing, variability due to effort dependence, and concerns around how a negative learning effect can impact values over time. Development and validation of methodology to enable patients to perform 6MWT remotely using smartphones, supplemented by provision of a pulse oximeter, is ongoing and may help overcome some of the challenges sites and sponsors face with test frequency, consistency, and logistics.

A Visit-by-Visit Look at a Hybrid Respiratory Trial

PPD Digital can design and integrate these types of technology into your clinical trial while following our robust onboarding and due diligence process. Our goal is to provide with excellence in all aspects of trial delivery — with the addition of PPD Digital's decentralized expertise, we have the ability to take this to the next level.

Multi-Component Integrated Solutions

The COVID-19 pandemic has accelerated innovation across all therapeutic areas — but most specifically around how remote technology can improve the patient experience, site interface, and patient health in clinical practice. Cystic fibrosis patient groups are at the forefront of this space and have created free apps that integrate data from multiple devices to build a holistic picture of the patient's status, potentially allowing for more timely identification of infections and earlier intervention. An example of this is Project Breathe by the Cystic Fibrosis Trust. The Project Breathe app

By Including DCT Solutions We Could Reduce in Clinic Visits by 50%

AT SITE VISIT 1 2	AT HOME VISIT 3	AT SITE VISIT 5 7	AT HOME VISIT 4 6 8	AT SITE VISIT 9	AT HOME EOS
Consent	Televisit/HNN	Vitals	Televisit/HNN	Vitals	Televisit/HNN
Screening	Dosing	ECG	Dosing	Bloods	
Inc/Ecl Criteria	Pre-Dose Bloods	Blood Draw	Pre-Dose Bloods	Physical Exam	
Randomization	ECG	PK/PD	ECG	Spirometry	
Physical Exam	ePRO	Physical Exam	ePRO	MRI	
MRI	*Remove MRI From Visit*	Spirometry			
		MRI			

digitally captures variables, including height, weight, temperature, heart rate, O^2 saturation, spirometry, sleep, and activity, as well as patient-reported outcomes (PROs). The addition of blood glucose monitoring and inhaler usage in the future could further expand the scope of variables captured, as well as the breadth of data sets.

Successful implementation of integrated digital solutions in the respiratory space, such as Project Breathe, should help sponsors gain the confidence to apply similar approaches within their clinical trials by providing the final reassurance that not only can it be done, but that it is also what clinicians and patients want.

Large data sets such as this could be powerful tools to demonstrate value to payers beyond conventional endpoints provided to support regulatory approvals.

Securing the Right Partner for your Respiratory Research

While we have seen a rapid adoption of DCT solutions over the last year, it is crucial that these solutions are applied selectively and are based on detailed knowledge of how technology could strengthen endpoint collection. Our consultants work closely with sponsors to tailor solutions to the program needs and guide stakeholders away from applying solutions just because the technology exists.

PPD balances technology and innovation with risk management to meet the needs of primary stakeholders: patients, sites, and sponsors. In the past five years, PPD has conducted more than 150 studies in respiratory medicine, reaching over 42,000 patients worldwide. We are continually leveraging our vast digital and decentralized clinical trial experience and subject matter experts to establish comprehensive, flexible options for respiratory clinical trials. Connect with our team to learn how your protocol could be digitally optimized for the future. ■

Tim Rich
Vice President, Consulting, Innovation & Strategy (CIS), PPD® Digital

Tim Rich serves as an Executive Director and founding member of PPD's digital and decentralized business unit. In this role, he oversees the consultancy group developing digitally enabled, hybrid, and decentralized trial strategies. Before his current role, Rich was a member of a biotech operational leadership group, where he provided strategic direction, leadership, and management across multiple divisions and therapeutic areas to ensure that a customized effective biotech delivery model is applied. His experience spans all elements of global project management, portfolio management, client relationship, and corporate strategy.

Email: tim.rich@ppd.com
LinkedIn: www.linkedin.com/in/tim-rich-96a66621/

Jenna McDonnell
Director, Consultancy, Innovation & Strategy, PPD® Digital

Jenna McDonnell currently serves as a Director for PPD® Digital, a dedicated decentralized trial business unit within PPD. She works within the consultancy, innovation, and strategy group, who are driving forward the adoption of decentralization while bringing forward innovative new solutions. Jenna joined PPD Digital in 2020, bringing with her 16 years of experience in clinical operations and digital and decentralized trials with a specific focus on electronic consent (eConsent) and electronic clinical outcome assessment (eCOA) technologies.

LinkedIn: www.linkedin.com/in/jenna-mcdonnell-54529a117/

Wesley Hicks
Vice President and Global Therapeutic Head, Respiratory,
Global Product Development, PPD

Wesley Hicks is vice president and global therapeutic head of respiratory at PPD. He works on behalf of biopharmaceutical and biotech clients, providing strategic medical oversight for clinical programs and advising on product development strategy and clinical trial design. With a decade of increasing leadership responsibility at PPD and earlier experience from respiratory clinical programs at GSK, Wesley has been involved in the construct and delivery of a wide range of respiratory programs spanning a variety of indications.

LinkedIn: www.linkedin.com/in/wesley-hicks-15841913/