MODERN STRATEGIES FOR DERMATOLOGY CLINICAL TRIALS

→ BY **ROSE BLACKBURNE M.D., JOHN MANNS, TIM RICH,** AND **MICHAEL NOSS, M.D.,** PPD

To be most successful, dermatology clinical trials should be accessible to a diverse array of qualified patients and designed to encourage patient participation. These trials should also reduce the patient and investigator site burdens, reduce start-up and enrollment timelines, and ensure consistent, high-quality assessments and data collection. With extensive experience in dermatology trials; an international network of sites with dermatology experience in key indications, such as psoriasis and atopic dermatitis; access to a large database of potential trial participants; and a commitment to tailored trial design and leveraging digital tools, PPD is ideally positioned to help sponsors rapidly and successful complete dermatology studies, even in the face of challenges posed by the COVID-19 pandemic.

ACTIVE CLINICAL SPACE

While advances have been made in dermatological medicine, including the development of novel biologic drugs, unmet needs remain in most non-malignant dermatological conditions, including acne, atopic dermatitis, psoriasis, rosacea, alopecia, and skin rejuvenation (wrinkle revision with dermal fillers or botulinum toxin products).

Widely available over-the-counter (OTC) and prescription topical corticosteroids are generally first-line treatments for psoriasis and atopic dermatitis, but they are not long-term solutions owing to issues with side effects. Similarly, biologic products are expensive and not always included in health insurance formularies, and there are variable country-level guidelines and approvals of different products.

In addition to more traditional topical products and novel injectables, drug companies are also developing oral medications. There is also significant development activity in biosimilar products for the treatment of

psoriasis and atopic dermatitis and growing interest in plant-based/botanical type products, including those based on cannabidiol (CBD).

The dermatology development landscape can be further segmented into consumer health (OTC) and prescription markets, the latter of which includes topical preparations of various types, as well as oral and injectable products that include non-biologic anti-inflammatory agents, biologics, and biosimilars.

As we move into 2021, a significant percentage of clinical trials underway will be focused on atopic dermatitis across all phases. While many of these trials involve new chemical entities or new biologic compounds, many are focused on extending approvals of existing products intended to treat other disorders of an immuno-inflammatory etiology, such as rheumatoid arthritis and other autoimmune conditions, as well as dermatological indications, including psoriasis, atopic dermatitis, vitiligo, and rosacea. With a number of biologics coming off patent, there is also heightened development activity around biosimilar alternatives.

An increasing number of studies will also be evaluating new medications for previously less-studied indications, such as epidermolysis bullosa (EB), vitiligo, urticaria, hidradenitis suppurativa (HS), and pemphigus. Notably, several early-phase trials are focused on treatments for wounds (e.g., diabetic foot ulcers), burns, and scars, as well as for alopecia, which has traditionally involved hair clinics and cosmetic centers.

Another important trend in the dermatology clinical space is the increasing use of technology for televisits, remote electronic consent, and other applications, with the COVID19 pandemic providing a real driver for uptake. As a result, teledermatology has gained more widespread use across the world for clinical consultation, patient assessment, and follow-up, with televisits of increasing interest in dermatology clinical trials as a way of reducing the study visit burden for both patients and trial sites.

PATIENT IDENTIFICATION AND ENROLLMENT CHALLENGES

With well over 500 dermatology clinical trials underway, there is intense competition for eligible patients, particularly in atopic dermatitis. Experienced dermatology clinical trial sites in Eastern Europe are rapidly approaching saturation in terms of identifying eligible subjects to meet trial enrollment targets. New and less experienced sites have to be identified and trained to meet clinical trial demands. Interest in trial participation also tends to wane in the summer and increase in the winter in response to a correlation between the severity of many dermatological conditions and the weather (symptoms are generally more severe in cold, dry seasons).

The nature of the drug and disease and the requirements of the trial can also impact patient motivation. Drugs that are easy to self-administer are preferential (topical, then oral). Injectable drugs that require self-administration or IV infusion in a clinic are less desirable. Similarly, studies that require intense pharmacokinetic/pharmacodynamic studies and frequent skin biopsies are more difficult to enroll.

There are also other study-related factors that increase the challenges to enrollment and study conduct. Study sponsors often want board-certified dermatologists to serve as investigators, though many patients consult their general practitioner first–a physician who may not have specific knowledge and experience in conducting dermatology clinical trials. Finding the right patients can also be an issue.

IMPORTANCE OF CONSISTENT ENDPOINTS

Because many endpoints in dermatology clinical trials are based on visual evaluation of the skin (e.g., plaques, flaking, redness, lesions, percentage of body surface area coverage) accurate, consistent, and objective assessments are crucial for these studies to succeed. The levels of detail and precision required for clinical trials are generally much higher with more rigorous patient evaluations than normally needed for general treatment.

Additionally, investigators and their teams at all participating sites must be trained according to the same procedures and protocols to eliminate the possibility of significant variance in assessments from site to site, and even physician to physician within the same site. Frequent retraining is also recommended. Where possible, patient visits should also be scheduled with the same investigator throughout the study to further ensure assessment continuity and consistency.

Evaluation of data for the placebo effect is equally important, particularly when patient-reported outcomes (PROs) are part of the study. The use of photography can introduce a measure of objectivity; however, these issues must be addressed during both site training and data analysis.

THROUGH PPD'S RELATIONSHIP WITH AES, OUR CUSTOMERS CAN RECEIVE 50–100% OF THEIR ENTIRE TRIAL ENROLLMENT FROM ONE ACCOUNTABLE SOLUTION, DELIVERED BY RESEARCH LOCATIONS THAT OPERATE UNIFORMLY ACROSS THE GLOBE.

ADVANTAGES OF DECENTRALIZED STUDIES

Traditional trials require patients to visit investigator sites for all physician interactions. Decentralized trials leverage a variety of digital tools and technologies to enable the completion of trial tasks that normally involve face-to-face interactions remotely without compromising efficiency. Moving to a decentralized model shows promise in mitigating some of the burden and cost of traditional methods while preserving the quality of oversight.

In the dermatology space, the large number of clinical trials in psoriasis has provided an opportunity to gain experience with digital solutions, including e-consent, televisits, and remote assessment using a variety of digital tools. Experience is also being developed in other indications where similar approaches can be used, including atopic dermatitis, alopecia, and vitiligo.

Indications where patients are healthy except for certain skin conditions, such as acne, are also well suited to decentralized trials. In indications such as burns and diabetic foot ulcers it is possible that, while some in-person interactions are required, certain assessments could be completed virtually.

Dermatology studies can include a number of PROs to assess the impact of the patient's disease on quality of life, where dermatological conditions can have a high burden on patients. The ability to report these via electronic PROs (ePROs) aids reporting of outcomes that patients may feel more comfortable reporting remotely rather than in person, such as more personal impacts of their diseases, including perceived quality of life, mood, and other outcomes. Furthermore, by combining all of the digital tools on one platform – ePROs, video conferencing, uploading of digital photographs, etc. – the burden on the patient, as well as on the site, can be reduced even more. The ability to provide patient reminders and check data in real-time also ensures higher levels of compliance and better-quality data.

Digital technologies also have the potential to improve the current high failure rate for screening potential trial participants. These could take the form of a prequalification questionnaire provided by text or email that covers key criteria that must be met. It could also include site staff of the investigator having a video chat with the patient using his/her personal desktop or mobile device.

Such an approach would provide clarification without requiring the patient to travel to the investigator site and help identify those with the best chance of qualifying. The end result would be a reduced screen failure rate and thus a reduced site burden and cost. Ineligible patients would avoid a trip to the clinic, saving time, cost, and inconvenience, while also avoiding potential exposure to the flu, COVID-19, and other illnesses.

A COMPLETE ECOSYSTEM OF CAPABILITIES

PPD is more than a contract research organization. Our Accelerated Enrollment Solutions (AES) business unit offers best-in-class site and enrollment solutions, providing greater speed, certainty, and control to clinical trial delivery through a global pay-for-performance patient-enrollment engine and standardized global site infrastructure that provides centralized and consistent operations and quality worldwide. Through PPD's relationship with AES, our customers can receive 50–100% of their entire trial enrollment from one accountable solution, delivered by research locations that operate uniformly across the globe.[1]

With a huge footprint of investigator sites – including both owned (AES sites) and partnered (PPD network) sites worldwide, PPD has established extensive expertise. Our project managers (PMs), clinical trial managers (CTMs), and clinical research associates (CRAs) are highly experienced and ready to tackle any obstacles your research might face. We also have a large pool of fully audited and approved vendors that are readily available to support studies without the need for vetting.

PPD continues to build out areas of expertise to ensure that we provide sponsors with the highest-quality, most efficient clinical study design, management, and operations. For instance, PPD continues to expand site networks to enable higher enrollment rates by focusing on high-performing site relationships and seeking ways to overcome the seasonality effect associated with dermatology trials, including leveraging sites in both the Northern and Southern hemispheres so that subjects can be enrolled continuously despite seasonal changes in individual countries.

With teledermatology on the rise, the PPD Digital team is further developing various digital approaches that leverage our partnerships with industry-leading decentralized trial platforms.

Decentralized trials are not one-size-fits-all. With trusted consultants from PPD® Digital, a determination can be made on which technology or platform is the best fit based on the needs of sites, sponsors and patients. We evaluate each trial carefully, considering the region, protocols, endpoints, regulatory constraints, and many other factors to determine what options are best for the sponsor. This thoughtful approach to strategic planning and study implementation based on a thorough analysis of all relevant data ensures that the most optimal solution is designed and deployed for each trial and customer.

GET STARTED WITH THE RIGHT TEAM

PPD has a unique position in the dermatology clinical trial space, having conducted more than 40 dermatology studies in the past five years that have involved nearly 700 investigators and greater than 10,000

Case Study: Rapid Rescue and Decentralization

The need for digital and operational tools that can rapidly support a transition from a traditional to a decentralized clinical trial has never been so acute as when sponsor companies came to grips with the impact of the COVID-19 pandemic. However, combining the resources of PPD's vast network, and our clinical operational, regulatory, and data privacy teams, we are able to develop custom solutions even under the tight timelines and increased pressure of the rescue of a dermatology clinical trial.

In one example, a dermatology clinical trial requiring the collection of several primary end points via in-person clinic visits was successfully underway in Italy when the pandemic hit. The Italian government mandated stringent controls to restrict the movement of people within the country, which would have prevented five patients from attending their final visits, and thus the collection of the primary end point data from these patients.

In order to save the clinical trial, it was necessary that a 21 CFR Part 11–compliant digital solution be implemented as fast as possible. In a matter of weeks, the PPD Digital team deployed a visual communication tool using the TeleVisit lite module — itself developed in response to COVID-19 — to facilitate investigator and patient interaction and consent issues, which allowed all patient assessments to be conducted as planned.

PPD CONTINUES TO BUILD OUT AREAS OF EXPERTISE TO ENSURE THAT **WE PROVIDE SPONSORS WITH THE HIGHEST-QUALITY, MOST EFFICIENT CLINICAL STUDY DESIGN, MANAGEMENT, AND OPERATIONS.**

patients. We have extensive experience with psoriasis, atopic dermatitis, pemphigus, and glabellar lines. Our dermatology experts regularly work with both large biopharma companies and small/emerging pharma and biotech firms.

PPD has invested heavily in the dermatology therapy area, and we understand the importance of selecting the right sites that can capture the right patients and use rater scales consistently. For our dermatology studies, PPD ensures that all investigators are experienced dermatologists with proven success in enrolling the right patient population and thus ensure quality data collection across the participating sites.

We also recognize that a standardized training plan must be developed and implemented at the study team and site levels. By having properly trained sites and staff, the quality and integrity of the data collected in studies will be preserved. PPD has developed a comprehensive training program leveraging our dermatology toolkit to educate our CRAs and site staff so that all studies produce the quality data required for regulatory compliance. We also leverage our partnerships with companies that offer technology-based rating-scale training in order to minimize assessor variance.

Furthermore, the AES network includes dedicated sites with dermatology experience in the United States and EMEA, and there are over 6 million pre-screened dermatology patients listed in the AES database. Our experience in dermatology, combined with access to this large network of sites, has enabled us to gain tremendous efficiencies. Sites are activated more quickly, allowing for faster than expected onset and completion of enrollment than expected, leading to time and cost savings.

A key differentiator for PPD is the investment we make in building a strong rapport between our sites and PPD's clinical teams, which helps to motivate sites to follow directives and complete requests during critical time periods, such as advanced, detailed planning of monthly data cleaning and review activities. Our collaborative approach creates a high level of cooperation across all PPD Functional groups and with sponsor counterparts as we all work towards the common goal of successfully implementing and completing high-quality trials that will enable needed medicines to reach the market.

As the clinical landscape continues to evolve, PPD has the resources to conduct trials in many ways, including traditional, hybrid, and decentralized trials, in the dermatology space. Our experience with eCOA, ePRO, telemedicine approaches, hybrid virtual trials, e-consents, electronic medical records, and remote source document verification (rSDV), among others, has enabled us to rapidly convert traditional trials to decentralized trials during the COVID-19 pandemic. Indeed, our experience, pooled knowledge, and access to the AES database of patients has allowed PPD to quickly pivot in response to unexpected and changing situations, providing the support and insight needed to address heightened risks and keep trials on track.

EXPANDING PATIENT ACCESS

Quality clinical trials cannot be achieved without the participation of qualified patients. Given the difficulties in finding these patients and the challenges patients themselves face in accessing dermatology clinical trials, PPD has taken several steps to help address these issues.

First, we expanded our country and site footprint – including both AES sites and others in the PPD network – with strong dermatology capabilities in the United States, Hungary, Poland, the Czech Republic, Serbia, Croatia, Italy, Belgium, Denmark, Israel, India, and South Africa. Efforts are also ongoing to train primary care providers so that they are equipped with the knowledge needed to recommend patients for clinical trials. Inclusion of non-specialist sites with solid trial experience provides greater access to potential patients who often first seek help from their primary doctors.

We have fully leveraged PPD's in-house medical expertise networking together our dermatologists and dermatology dedicated physicians across our functions from product development to pharmacovigilance through to AES site personnel.

To reach potential patients, our teams continue to create global awareness through a unique blend of various media platforms, webinars, and other forums.. At the same time, we continue to innovate to accommodate evolving study needs, including the use of digital and/or remote patient and site activities.

We look at each trial individually to consider potential problems, such as seasonality and the placebo effect. We also seek to understand how the medication will be administered (topical, oral, injectable) and how that will impact interest from different patient groups. PPD teams also put themselves in the shoes of the patient. For instance, thinking as deeply as whether or not women will reject participating in a trial with a topical medication that must dry for two hours before they can apply makeup. Or, in other cases, groups may not participate if the drug is an injectable that must be administered in a clinic.

Because dermatology conditions like psoriasis, atopic dermatitis, and acne are not life-threatening, clinical studies must be designed so that minimal burden is placed on the patient throughout the course of treatment. On the other hand, given the significant impact that these diseases can have on quality of life – depression, low self-esteem, poor performance due to psychological effects, lack of sleep, etc. – patients can be highly motivated if a study is well designed. Therefore, it is essential to leverage new technologies as much as possible and work with sites that are specially equipped to work with this unique patient population, thereby generating excitement to participate in interesting and treatment-advancing clinical research.

LOOKING AHEAD AS ADOPTION INCREASES

The COVID-19 pandemic has accelerated the adoption of virtualized and decentralized trial protocols. Telemedicine and teledermatology are not new; dermatologists were using digital technologies to reach patients in areas where specialists are lacking long before the emergence of the SARS-CoV-2 virus. The pandemic has, however, pushed the development of new technologies and advanced versions of those that already existed specifically for use in clinical trials.

The goal of clinical studies for sponsors is to prove to regulators that their products are safe and effective to distribute to patients in need. It is hoped that wider use of the decentralized trial model during the COVID-19 pandemic will provide evidence that remote assessments and collection of dermatology endpoints can provide the same quality data as those obtained via on-site visits. In addition, accessibility and enrollment can be improved while the burdens on the patient and the investigator site are reduced.

Indeed, the current situation has presented a tremendous opportunity to compare results obtained using traditional on-site protocols with those collected remotely using a combination of digital tools. So far, at least one satisfaction survey has revealed that both patients and physicians feel that the quality of care and results obtained during televisits is equal to that of onsite visits. We also have the opportunity to produce early benchmarks for the accessibility of virtualized and decentralized trials and the impact that digital technology has on key components such as diversity and recruitment.

Going forward, we expect sponsors to start pushing for the use of hybrid solutions with a combination of site-based and remote activities as they seek to meet the evolving needs of patients around the world. P

Note: additional insight provided by: Phil Pickford, Senior Director, Project Management, PPD; Norma Cantu, Senior Director, Project Management, PPD; Annika Dhondt, Executive Director, Project Management, PPD; and Cristina Nieto, Vice President, Project Management, PPD.

REFERENCE

1 *PPD's Accelerated Enrollment Solutions Acquires Global Site Business from Bioclinica.* PPD. 9 Sep. 2019. Web.

ABOUT THE AUTHORS

John M. Manns
Senior Director, Innovation and Digital Operations, PPD® Digital

In his current role, **John** provides vision and strategy on planning and executing decentralized clinical trials to solve operational challenges, particularly where there is a benefit to the patient. John brings more than 25 years of industry experience, including leadership positions in PPD's innovation and operational teams. John holds a Bachelor of Science degree in mathematics from the State University of New York at Cortland.

LinkedIn www.linkedin.com/in/john-manns-2868174/
Email john.manns@ppdi.com

Tim Rich
Executive Director, Decentralized Services, 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.

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

Rose Blackburne, M.D., MBA
Executive Medical Director, Global Product Development, PPD

Dr. Blackburne is a board-certified physician and experienced healthcare executive. As an industry leader, her career in healthcare spans over 25 years, including clinical practice, direct patient care, health management, and most recently as an executive in pharmaceutical, biotechnology, and medical device product development. Dr. Blackburne earned her medical degree from the Morehouse School of Medicine and an MBA from the University of Virginia Darden Graduate School of Business. Dr. Blackburne serves as Industry Representative Alternate (2016–2021) to the FDA Patient Engagement Advisory Committee (PEAC) to provide advice on issues relating to the regulation of medical devices and their use by patients and to develop agency guidance and policies.

LinkedIn www.linkedin.com/in/rose-blackburne-md-mba-516826a/
Email Rose.Blackburne@ppdi.com

Michael Noss, M.D.
Senior Director of U.S. Medical Operations, Accelerated Enrollment Solutions

Dr. Noss has been a principal investigator on over 700 clinical trials in more than 70 therapeutic areas. Throughout his career, he has developed a large dermatology niche that includes serving as a principal investigator on 27 psoriasis, six atopic dermatitis, 14 acne, four actinic keratosis, two cellulite, one keratosis pilaris, 11 onychomycosis, one seborrheic dermatitis, one seborrheic keratosis, and nine tinea pedis studies. In addition, Dr. Noss has conducted 88 consumer-based clinical trials, including product use and tolerance, dermal patching studies, biopsy, and much more.

LinkedIn www.linkedin.com/in/michaelnoss/
Email michael.noss@globalaes.com