PRECISION & SPECIALTY MEDICINES' IMPACT ON THE FUTURE OF CLINICAL TRIALS

Value Creation Strategies in the Future Clinical Trial Ecosystem

CROSSTREE

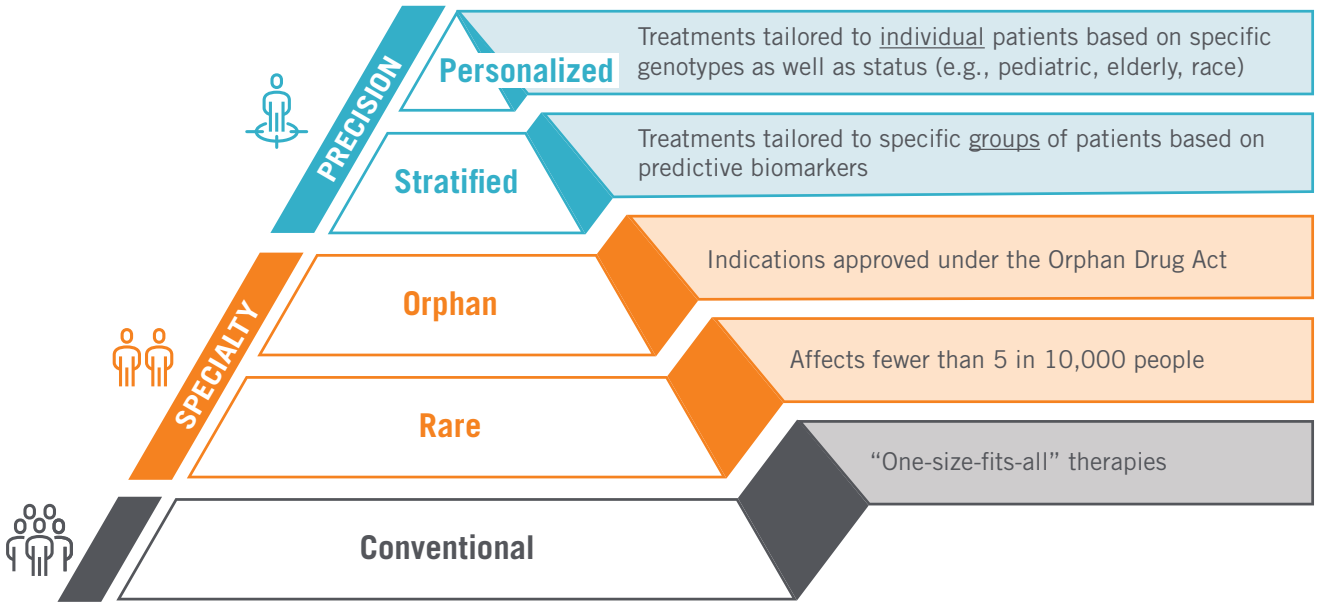
Table of Contents

Introduction

The pharmaceutical industry continues to evolve from a model focused on development of blockbuster drugs for large patient populations to one that addresses more specialized, complex treatments and patient journeys, tailored to each therapy in the case of Specialty Medicine, and to each patient with Precision Medicine. The demands of these two fast-growing categories of medicine are proving disruptive to established incumbents across the pharmaceutical development industry.

Due to Specialty and Precision Medicines radical departure from traditional models, the impact of its growing prominence is driving significant changes across the pharmaceutical development industry. In this paper, we will define the Precision and Specialty Medicine markets and explore the changes the impact these paradigms are having on one particular segment of the pharmaceutical development ecosystem - the clinical trial space. These changes present significant opportunities for value creation across the clinical trial space for financial investors who understand the implications of these shifting dynamics. Leveraging Crosstree's extensive expertise in these areas, we will also provide outlines of three distinct inorganic growth strategies which financial investors can deploy to capture future value in the clinical trial space.

Defining Precision & Specialty Medicines



PRECISION MEDICINE

Precision Medicine helps in the prevention as well as early diagnosis of patients, looking at the expression of genes or proteins and thus predicting response to specific medicines.[1] Thanks to a confluence of cultural, technological, regulatory, and economic factors, advancements in Precision Medicine have skyrocketed in the past few years, and the market has blossomed into one of the highest growth segments of the healthcare industry, valued at ~$60 billion today and projected to grow to ~$100 billion over the next five years and close to $800 billion by 2028.[2]

Stratified Medicines require the use of predictive biomarkers to identify patient response or suitability to therapies. Individual patients in the patient group receive identical treatments. The bulk of Precision Medicines are Stratified Medicines.[3] An example is Depakote®, used to treat epilepsy and bipolar disorder, which has the largest volume among the stratified CNS therapies.

Along with Stratified Medicines, Personalized Medicines also fall under the Precision umbrella. These medicines are tailored to individual patients based on specific genotypes as well as status (e.g., pediatric, elderly, race). Personalized medicines include gene therapies and many (but not all) immunotherapies.

SPECIALTY MEDICINE

Specialty Medicines are those medicines that (i) treat rare diseases, (ii) are classified as orphan drugs by the Food and Drug Administration (FDA), (iii) require special handling due to low volume, cold-chain, or other storage requirements, or are managed through separate organizational or delivery channels, including specialty pharmacies, (iv) are difficult or complex to manufacture on a consistent basis, or (v) require additional monitoring by a physician or are required to be initiated by a specialist.

Comprising both injectable and non-injectable drugs, Specialty Medicines are used to treat chronic, complex conditions.[4] These medicines have characteristics that can include: limited distribution network(s), close patient monitoring, requirements for special handling, complex formulations and/or manufacturing techniques, high costs per unit, and use in small or unique patient populations.[5]

Most often, Specialty Medicines are used to treat rare diseases. Crosstree has adopted the National Institutes of Health (NIH) definition of rare disease as one that affects fewer than 200,000 people in the United States, and further expands the definition to include diseases that affect fewer than 5 in 10,000 of the general population globally. There are nearly 7,000 rare diseases, and more than 25 million Americans have one. Roughly 3.5-5.9% of the global population is affected by a rare disease, which equates to 263-446 million persons affected at any point in time.

Rare diseases are acute or chronic in nature and may be considered life-threatening. They include cancers such as childhood cancers and some other well-known conditions, such as cystic fibrosis and Huntington's disease. Significant research is still required to learn more about the pathophysiology and natural course of these diseases, and epidemiological data remain limited or not available in many cases. Drug recovery costs are less in the case of rare disease for pharmaceutical companies, so, clinical trial funding programs continue to be an essential component motivating orphan drug development.

The distinction between rare disease medicines and orphan drugs is a small one, and the terms are often used interchangeably. Crosstree defines orphan drugs as those medicines with one or more indications approved under the 1983 Orphan Drug Act (ODA) — which includes drugs for rare diseases and also for other indications, essentially drugs that cannot be manufactured and marketed profitably. Crosstree further expands this category to include those drugs associated with a patient pool of less than 0.1% (for the U.S.); this may include drugs approved for non-orphan indications.

There is an inverse relationship between the price of these therapies and their volume of use: Orphan drugs are developed for small patient populations, making them expensive for both patients and payers. For example, the median annual cost for an orphan drug in 2017 was over $46,800, while the median annual cost for the top 10 disease therapies used by the greatest number of patients was $1,216. Thus, drug spending in the U.S. is progressing from a prominence on high-volume, low-cost drugs for chronic diseases to low-volume, high-cost drugs with higher value in terms of patient outcomes.

Precision & Specialty Medicines: Rise of Decentralized Trials

Precision and Specialty Medicines present a new slate of challenges for clinical trials, from patient recruitment to data management, necessitating new solutions and strategies. Chief among these strategies is remote or Decentralized Clinical Trials (DCT), defined as studies "executed through telemedicine and mobile/local healthcare providers, using processes and technologies differing from the traditional clinical trial model."[2] It should be noted that traditional and decentralized trials are not mutually exclusive: many trials become hybrids with some clinical trial activities taking place at the investigator site and some remotely. The design and implementation of DCTs need not be an "all-or-nothing" approach. A decentralized strategy may not include a central trial site but include visits conducted via telemedicine or by mobile or off-site healthcare providers and the use of mobile technologies to record data.

Decentralized studies are not bound by the geographic limitations that affect traditional trials, enabling greater patient recruitment and more frequent - even continuous - measurements because they are not restricted by scheduled clinic visits. To support the adoption of DCTs, almost all US states now have telemedicine laws that allow for mobile medicine.[3,4] For these reasons, explored in detail in this paper, pharma sponsors are increasingly employing decentralized strategies in their clinical studies: research conducted by Greenphire found that 84 percent of sponsors and CROs are actively seeking to increase their use of technology to better support DCTs.[5]

Precision & Specialty Medicines' Impact on Clinical Trials

Precision and Specialty Medicines' impact is felt across the clinical trial space, creating significant challenges in patient recruitment, trial design and execution, supply chain and logistics, and data management. Value creation for companies performing any one of these critical functions demands a nuanced understanding of the ways Precision and Specialty Medicines, and the decentralized and hybrid clinical trials they necessitate, are driving change - both today and in the future. The following section will explore both the causes and effects of these changes in each of the four areas.

PATIENT RECRUITMENT

Precision and Specialty Medicine clinical studies are directed at specific subpopulations of patients with a certain - often rare - disease. As a result, the criteria for participating in a Precision Medicine or rare disease clinical trial are very narrow, limiting the number of patient subjects available. Unlike traditional clinical trials which can utilize general practitioners to recruit all the patients needed for the study, Precision and rare disease trials must go to specialists located all over the country and even the world, often seeking a patient pool that's never been targeted before. Further compounding patient recruitment challenges, in Precision Medicine trials specifically, is the fact that target patients may be unaware of their disease state, never having been tested for the study's subtyping before.

The **specialized protocols** needed for the complex standard of care in these cases is driving other requirements in decentralized trials to enable **last mile connection** with patients.

Precision and rare disease trials must also often accomodate limited patient mobility. Studies require patient-provider interactions, and these are difficult with patient populations with special needs such as physical disabilities or compromised immune systems which preclude or hinder travel to trial sites.

The specialized protocols needed for the complex standard of care in these cases is driving other requirements in decentralized trials to enable last mile connection with patients. These interactions must often be remote, meaning the doctor or nurse goes to the patient's home or even entirely virtual. As a result, new, innovative technologies are emerging to enable successful remote patient recruitment and engagement.

SUPPLY CHAIN AND LOGISTICS

Precision and Specialty Medicines trials' small, diffuse participant pools typically necessitate decentralized study design and global reach to achieve adequate patient sample sizes. The execution of any clinical trial requires various logistics solutions, ranging from delivery of drugs to providers and patients, procurement of supplies such as lab kits, medical devices, and printed materials to transportation and storage of biological samples with chain of custody documentation and tracking. However, compared to traditional clinical trials, decentralized and hybrid trial models result in more complex logistics and supply chains.

In traditional studies, drugs are delivered to trial sites which manage distribution to patients on-site In a decentralized or hybrid trial, drugs often must also be delivered to a patient's local pharmacy or directly to their home, for the reasons outlined above. When the study involves a global participant pool (a typical scenario, as outlined above), these deliveries must occur not just in a single metro area, but all over the world, including in third world countries where a lack of infrastructure renders traditional distribution methods difficult and often impossible. Thus, decentralized and hybrid trials must rely on technology to allow direct interaction with patients, informing them when the drug is ready to be picked up or is on its way to their home, because there is no provider intermediary to do so. Myonex, a global clinical trial solutions provider, is one company offering supply solutions for decentralized trial strategies.

Decentralized and hybrid trials must rely on **technological solutions** to enable drug distribution to patients when practitioners and traditional sites are not viable solutions.

Precision and Specialty Medicine study sponsors and CRO's must ensure study execution and quality of service delivered in every country is as identical as possible within a patchwork of regulatory frameworks. Successful supply chain execution for these studies requires an understanding of the clinical trial process from a global perspective, and regulatory and trade compliance teams must determine optimal import and export processes as well as plan for ancillary procurement, storage, and supplies. Solutions which enable these complex trial supply chains include consolidated clinical storage, distribution, and logistics networks; global GMP depot networks; project management teams with GMP, GDP, logistics, and DTP experience; global study management platforms; and real-time track-and-trace technologies with monitoring and reporting of drug and sample location, temperature, and other condition elements.

TRIAL DESIGN AND EXECUTION

Traditional studies can also easily utilize an adaptive trial strategy, where multiple trial protocols are used concurrently to determine which works best, and the better protocol then deployed throughout the rest of the trial. In decentralized and hybrid trials with smaller population bases, it's difficult and very costly to run an adaptive trial, so it is necessary to have near real-time data to enable fast decision-making and

DEAL INSIGHT

OVERVIEW

WCG acquired Los Angeles-based Trifecta Clinical to bolster its remote study startup and compliance support offerings.

SIGNIFICANCE

WCG is an industry leader delivering transformational solutions for clinical trials. They provide services that foster compliance and maximize efficiency for those in science and medicine, empowering their mission to develop the therapies and medicines that improve quality of life. By acquiring Trifecta, WCG adds remote study startup and compliance support to its suite of "Smart Trial" solutions.

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reduce costs. As a result, data interoperability, the timing of clean data, and the data standard in which trial data is stored become critical to the successful execution of these complex protocols.

> **Data interoperability**, the timing of **clean data**, and the **data standard** in which trial data is stored are critical to the successful execution of **complex hybrid protocols**.

The geographic dispersion of small patient pools and the scarcity of relevant medical experts in Precision and Specialty trials typically necessitates multiple sites, remote solutions, and multinational collaboration. The latter presents a whole host of challenges, as regulatory requirements vary dramatically across (and sometimes within) countries. Trial design for global patient populations must comply with these various regulations while maintaining consistent protocols that ensure comparable study data.

DATA MANAGEMENT

In traditional studies, in-person source data verification (SDV) is a cost-effective approach due to high patient concentration at trial sites. In decentralized studies, sites serve very few patients each and are often spread across several countries, rendering this approach unviable. Instead, decentralized and hybrid trials must rely on risk-based and central monitoring. which necessitate data monitoring committees to ensure signals are detected and addressed. In these scenarios, data interoperability, the timing of clean data, and the data standard in which it's stored are critical concerns. These demands strain existing biometrics capabilities, increasing demand for new technologies to enable these protocols.

As Precision and Specialty Medicine moves more trials to decentralized and hybrid strategies, concerns about data reliability and quality with remote data collection are being raised by sponsors.[6] New patient- and investigator-facing technologies have arisen to mitigate accuracy risks[6], but adoption of these technologies has increased complexity of processes required for data quality. The use of mobile apps, ePROs, and wearable monitoring devices improves convenience for patients, provides real-time data, and reduces site burden, but also requires additional training, technical integrations, and analysis to ensure regulatory compliance.

In DCTs, data is often communicated between and stored among several different parties, locations, and systems, adding layers of data privacy concerns which must be addressed, a particularly complex undertaking at global scale. Sponsors and CROs must establish clear protocols for data sharing both within and between countries with different data privacy laws. While regulators in the U.S. have expressed support for DCTs and are working to provide guidance to help overcome data privacy challenges, restrictions in other

countries can create complexity for global Precision Medicine and Specialty trials. The European Union's General Data Protection Regulation (GDPR) requires participants to provide consent prior to a sponsor reviewing and using a participant's data in clinical trials, and sponsors to carefully consider what personal data study teams collect, how that data is processed, and what records are necessary to demonstrate GDPR. In addition, each EU country has its own national data protection authority (DPA) overseeing the application of GDPR and other privacy or data protection requirements in that country.

Because global DCT sponsors' trial plans must incorporate the requirements and guidance from GDPR and the DPAs, technology platforms are being actively adapted to adhere to GDPR regulations. Sponsors must be able to prove compliance to various supervisory authorities, regulatory bodies, and often ethics committees of their data management protocols and technologies. To help meet this growing need, regional and global trial execution consultancies have developed in order to provide comprehensive regulatory, clinical, and compliance expertise for sponsors and CROs.

As we've outlined in this paper, Precision and Specialty Medicines' growing prominence is driving significant changes across the clinical trial space. Fortunately, these changes present significant opportunities for investors. Here, we explore three strategies for successful value creation in this new paradigm.

DEAL INSIGHT

OVERVIEW

pharmasol was Acquired by PharmaLex to Offer Turnkey End-to-End Pharmacovigilance Solutions.

SIGNIFICANCE

pharmasol is a leading global life sciences services organization providing tech-enabled pharmacovigilance solutions. The company provides automated data management, warehousing, and reporting, making their technology the perfect complement to PharmaLex, one of the leading pharmacovigilance consultancies in the world and a key opinion leader and subject matter expert in pharmacovigilance and safety.

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Value Creation in the New Paradigm

ACQUIRE CAPABILITIES TO EXECUTE GLOBALLY

Decentralized and hybrid global trials supporting Precision and Specialty Medicine are the future of drug development, regardless of where a company operates within the clinical trial execution space. Whether a platform provides technology, logistics services, or consulting, global infrastructure and capabilities will be essential to future value creation. Sponsors and CROs will continue to seek ways to streamline execution and consolidate vendors. In this market, single source providers with global reach and expertise will capture significant advantage over those with only national capabilities. Greenfield expansion is possible, but as the drug development space evolves so rapidly, inorganic growth through acquisition of targets with similar capabilities in targeted geographies will allow platforms to scale faster and capture first-mover advantage.

ACQUIRE TECHNOLOGY TO ENABLE REMOTE SERVICES

As Precision and Specialty Medicine drive more trials to decentralized models, nearly all aspects of these studies must be executable remotely. Platforms which acquire the necessary technological capabilities to enable remote trial execution can create value through both future revenue growth and stability and reduced operating costs. One clear example is clinical trial sites adapting to the Precision Medicine paradigm where centralized physical sites are less relevant. Trials with fewer in-person visits can allow sites to offer sponsors new and enhanced participant engagement tactics to optimize the remote participant experience. Technology that facilitates virtual visits, such as secure video conferencing, is critical for successful execution of remote trials, allowing sites to remain competitive, and offers sites the additional benefit of reduced in-person monitoring costs. Integration of these technologies with Clinical Trial Management System (CTMS) or EHR systems also helps streamline workflows and reduce data entry requirements, further reducing costs.

Platforms which acquire remote technology can accelerate their transition to the Precision and Specialty Medicine clinical study model while improving operational efficiency. For example, traditional clinical trials rely on paper-based patient consent forms. As one can imagine, management of these forms is time-consuming, rife with risk of data loss and errors, and impractical for remote trial models. Electronic consent or "eConsent" systems digitize patient informed consent processes, helpful in all trials but particularly critical in decentralized models when participants never physically enter a site.

Platforms can also make themselves globally competitive through technological capability acquisition Navigating the regulatory frameworks of a single country in a traditional clinical trial is complex enough, but successfully managing requirements of multiple countries in remote studies adds multiple additional layers of complexity. Clinical trial sites typically maintain a binder of physical regulatory documents created before, during, and after clinical trials to ensure compliance. eRegulatory management systems offer an electronic version of this binder, facilitating digital compliance and information sharing with sponsors and CROs.

ACQUIRE ADJACENT CAPABILITIES TO REDUCE COMPLEXITY IN DCT EXECUTION

Significant inorganic growth opportunities also exist for companies with existing global footprints and/or remote technologies in the form of adjacent capability acquisition. As sponsors and CROs look for ways to optimize and simplify complex Precision Medicine studies, vendors offering comprehensive support will enjoy competitive advantage over those with limited specialized service capabilities. For example, established global regulatory and compliance with eConsent and eRegulatory technologies can acquire or partner with trial execution and logistics firms to offer customers an integrated solution that simplifies data sharing and helps ensure smooth study operations.

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CONCLUSION

A variety of cultural, technological, regulatory, and economic factors are accelerating growth in the Precision Medicine segment to an expected $800 billion by 2028.[1] Specialty Medicine and rare disease trials continue to fuel this paradigm shift, driving significant change in clinical trials as smaller, more targeted participant populations demand decentralized global study models. These changes offer financial investors three distinct paths to value creation for portfolio companies operating in the clinical trial space: geographic expansion, move to remote services, and acquisition of adjacent capabilities. While each of these paths can be executed organically, the rapid pace at which the Precision and Specialty Medicine market is growing and advancing will offer significant first mover advantage, making inorganic growth strategies more attractive. In addition, the sheer volume of potential acquisition targets in the clinical trial space will allow financial investors a variety of options to execute on these strategies by leveraging the deep market insights of specialized financial advisors, such as Crosstree.

About Crosstree

As one of the leading investment banks in pharma services, Crosstree combines data, financial analysis, and an in-depth industry knowledge with real-world execution experience. Crosstree's consultants, advisors and bankers work with a world-class network of industry experts, executives, and investors in order to help formulate and execute the most accretive transactions possible for our clients. No other advisor has a deeper understanding of how the confluence of industry trends, market conditions, and growth opportunities will shape a company's value and strategic outcomes in the pharma services space.

Crosstree's deep expertise in pharma services, diagnostics and tools, and digital health provides an unprecedented advantage to prospective strategic partners in today's market. Because Crosstree works with such a comprehensive understanding of the pharma services industry, we can synthesize a company's capabilities, financial data, and market position to communicate a compelling value creation strategy or proposition to buyers, sellers, and other strategic partners.

Our Strategic Services team provides actionable plans and pragmatic guidance to create and realize greater value for our clients. By combining proprietary research, expert financial analysis, and industry knowledge with real-world execution expertise, Crosstree helps companies plan, evaluate, and execute viable in-organic growth strategies to achieve successful outcomes downstream.

In February 2021 Crosstree published its inaugural Innovations in Pharmaceutical Development™, a first-of-its-kind compendium of the industry's most innovative companies; a go-to resource of what is coming 2021 and beyond. Unlike other directories, this publication organizes the Pharma Services industry using Crosstree's proprietary and granular taxonomy, which helps define the industry in an easily understandable and concise way.

FIND OUT MORE

To learn more about Crosstree's Investment Banking and Strategic Services capabilities and life science expertise, visit CrosstreeCapital.com.

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