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Clinical trial conduct in special populations and developing regions: An overview of the DOVE study in pediatric patients with sickle cell disease

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ABSTRACT

Clinical trials conducted in unique patient populations or individuals with rare diseases are typically hampered by limitations in availability of qualified patients, requiring sponsors to broaden their global outreach to achieve enrollment. Engaging clinical study centers in developing regions may offer access to a substantially larger patient pool. However, they provide a unique set of challenges based on local cultures and requirements. The DOVE study (Determining effects Of platelet inhibition on Vaso-occlusive Events) was a clinical trial of prasugrel hydrochloride (prasugrel) in pediatric patients (aged 2 to < 18 years) with sickle cell anemia. The study was conducted at centers located in both well-developed and developing regions, enrolling 341 children. Study planning and execution required careful consideration of cultural requirements in each region and implementation of additional trial initiation and execution processes to address those needs. Innovative strategies were employed to ensure global consistency and quality in study execution. Significant regional- and country-specific differences were observed in site activation and enrollment. Although site activation processes were more complex and slower in developing countries, enrollment rates were much higher, which helped mitigate the site activation delays and allowed significant contribution to complete study enrollment. Data quality and patient retention in developing countries were equivalent to those observed in more developed countries, further supporting the ability to successfully conduct high-quality global registration trials in those countries. This report provides an overview of the experiences in site identification, site qualification, enrollment, patient retention, and data quality assurance in the DOVE study.

1. Introduction

The conduct of clinical research has traditionally been focused in regions with highly developed healthcare networks such as North America and Europe. Over the past two decades, healthcare evolution in developing regions and technological advances have revolutionized the execution of clinical trials, enabling global outreach to access clinical trial participants. This development is particularly meaningful when conducting clinical trials for rare disease conditions or special populations, where access to qualified patients is severely limited. When evaluating the opportunity to conduct a study in developing regions, a combination of ethical, clinical, regulatory, and country-specific requirements plays a critical role in the decision-making process [1,2]. Regulatory review and approval cycle times, data quality assurance, standards for medical care, local practices, and ability to comply with Good Clinical Practice (GCP) standards are all important components of the assessment process. In this report, we describe techniques and methodologies that were used to successfully navigate the operational challenges in the conduct of a high quality clinical research study across diverse geographic regions.

This report describes experiences from a clinical trial conducted in children with sickle cell disease (SCD). SCD is one of the most commonly inherited genetic conditions [3]. The incidence is highest in regions near the equatorial belt, primarily in developing countries, but can be found throughout the world [4,5,6]. Although the disease presents symptoms in infancy, it persists throughout the individual's lifetime. It is characterized by sickling of deoxygenated red blood cells which makes them inflexible and induces abnormal interactions with leukocytes, platelets, clotting factors, and the vascular endothelium [7,8]. Subsequent vaso-occlusion can result in severe episodes of pain referred to as a vaso-occlusive crisis (VOC), which causes debilitation and often requires hospitalization Earlier reports suggest that platelet activation contributes to thrombosis and VOC [10,11], although multiple small studies that have investigated the impact of antiplatelet agents on the frequency or severity of VOC have been inconclusive [12].

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Prasugrel has been shown to irreversibly inhibit platelet activation and aggregation [13,14]. It was hypothesized that prasugrel may reduce platelet aggregation associated with SCD, thus reducing the incidence of vaso-occlusion. The DOVE study (Determining effects Of platelet inhibition on Vaso-occlusive Events) was a double-blind, placebo-controlled, multinational study of prasugrel in pediatric patients (aged 2 to < 18 years) with sickle cell anemia. While numerous studies have been conducted previously in this population, few have successfully completed and disseminated results [15]. The DOVE trial design and primary outcomes have been reported previously [16,17]. The study was conducted in 14 countries, including centers located in North and South America, Europe, the Middle East, and Sub-Saharan Africa. A total of 341 children were enrolled, representing one of the largest controlled clinical trials conducted in this population. Study execution required consideration of local and cultural requirements in each region and implementation of additional trial initiation and execution processes to address those needs. The following report provides a summary of the trial execution methodologies, differential regional strategies, operational challenges and their overall impact on the execution of the DOVE study.

2. Methods

2.1. Country selection

Following development of the study protocol, a detailed assessment of available historical clinical trial data was systematically analyzed using clinical trial design technology provided by Semio Clinical Services (now Quintiles Infosario® Design). Alternatively, data could have been collected by performing a detailed literature review of therapeutically relevant past trials. Protocol-specific criteria were utilized to identify potential regions, countries, and clinical research centers with the appropriate population prevalence and research experience to maximize enrollment capabilities.

2.2. Enrollment projection

Prior to study initiation, patient enrollment projections were conducted using site activation and enrollment rate assumptions based on a sample of prior clinical studies. Due to this rare patient population, disease state, and geographies involved, few directly comparable studies were available.

Using historical data assumptions in conjunction with projected country and site participation levels, Monte Carlo–based enrollment simulations were conducted using the Quintiles interactive Strategic Evidence-based Evaluator (iSEE) tool. The iSEE combines historical performance analyses with therapeutic and country-level experiences to semi automate the creation and visualization of strategies for project execution. By using this technique, patient enrollment projections over time can be visualized and understood as a probability rather than a single point estimate. For the DOVE study projection, 300 study iterations were performed. Each iteration resulted in one possible timeline scenario that could be achieved. By analyzing 300 overlaid iterations, the tool provided a range and likelihood of possible study timeline results. This information was utilized to validate country-level enrollment expectations and guide final country and site selection assumptions.

2.3. Site selection and qualification

A rigorous site selection process was developed specific to this trial. The process focused on ensuring that the unique requirements of the trial were understood and assessed. Key decision points were put in place to facilitate site selection and proactively mitigate potential risks. The decision-making pathway is illustrated in Fig. 1.

A site qualification questionnaire was developed based on the study inclusion/exclusion criteria and were used to assess each site's capabilities, experience and interest. Assessments included but were not limited to the following key focus areas:

- Standards of care for sickle cell VOC and acute chest syndrome
- Use of intravenous fluids, narcotics, and nonsteroidal anti-inflammatory drugs for VOC
- Close proximity to emergency care (blood bank, emergency room, neurosurgery access, computed tomography scanning)
- Transcranial Doppler experience/access
- Cold chain storage (refrigerated, stored at 2–8 °C) for investigational product (IP)
- Experience in Phase 3 clinical research
- Experience in SCD research
- Documented availability of pediatric patients with genetically confirmed SCD diagnosis
- Percentage of patients with 2 or more VOCs or acute chest syndrome (ACS) crises within the prior year
- Adequate internet and computer access to satisfy study requirements, including capability to utilize electronic devices for collection and transfer of patient data

The ability to safely access the site and the country was also assessed as an additional consideration in some regions. A sponsor medical representative reviewed the completed assessments to ensure proper site qualification, capabilities, and global consistency.

Bioethics has previously been identified as an area of concern in developing regions [1,18], therefore, stringent requirements for site and Ethics Review Board (ERB) evaluation were applied for each participating site, a separate research ethics assessment was completed by the principal investigator (PI), the ERB, and the clinical research associate (CRA) monitor to demonstrate that the ERB had the appropriate GCP training and qualifications. Each PI and ERB were required to submit written verification that the site's ERB was qualified and met the International Conference on Harmonization (ICH) standards of clinical research.

Assessment of each country's regulatory process was performed to ensure consistent global application of ethical standards, including confirmation that established regulatory processes existed to enable the sponsor to pursue making the IP available to participants following successful completion of the trial. Each country's regulatory authorities and each site's ERB requirements were assessed to ensure no excessive translation requirements (unique dialects for patient-facing materials), no country-specific protocol amendments required, and no recruitment restrictions based on local or cultural requirements that may bias the population sample.

2.4. Site activation

Following selection, an on-site site selection visit (SSV) was performed, to ensure that the site personnel could appropriately conduct the study per the protocol specifications. If the sponsor or Clinical Research Organization (CRO) had information regarding recent experience at the site with the same PI within the prior year, a telephone assessment was conducted.

Site-specific research agreements were established and maintained throughout the study to govern compliance with study conduct and GCP requirements. On-site visits were conducted by sponsor personnel in each participating country during the course of the study enrollment period to ensure site facilities were adequate and study conduct was administered per the sponsor specifications. Additional on-site training was provided as deemed necessary for site personnel or upon request.

2.5. Patient recruitment and retention

Patient vulnerability has also been identified as an area requiring additional vigilance in developing regions [1,18]. As the DOVE study