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Development of a Prospective Real-World Data Clinical Registry of Children and Adolescents With Migraine

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Abstract

Objective: To develop a multicenter, multistakeholder, prospective clinical registry of children and adolescents with migraine to support the collection of real-world data of sufficient quality to support regulatory submissions and provide site-based infrastructure support for future clinical trials.

Background: As new migraine treatments come to market, pediatric efficacy and safety trials of these agents are needed. A clinical registry is an ideal regulatory strategy to provide both real-world data and site infrastructure to execute these trials.

Design: Multicenter, multistakeholder, prospective real-world data clinical registry of children and adolescents, 4 to 17 years of age, diagnosed with migraine with or without aura. Participants will be followed for up to 12 months at 3-month intervals, with interval recording of clinical data at study sites and self-reported data via mobile health application, as well as biobanking. We developed electronic case report forms that incorporated routinely collected clinical data with National Institute of Neurological Disorders and Stroke Headache Common Data Elements (Version 2.0). All data are captured in a 21 CFR Part 11–compliant electronic data capture system,

augmented by a real-time, web-based, and customizable data visualization platform. We engaged vendors to provide ancillary biobanking, patient data entry, and data visualization services.

Results: We used an iterative and highly collaborative multistakeholder approach to design and implement a streamlined registry protocol with input from all participating U.S. sites. At each design and implementation step, we received input from therapeutic area experts, the U.S. Food and Drug Administration (FDA), the National Institutes of Health, patient and parent advocates, health technology partners, drug developers, and site-based clinical investigators. The registry is governed by a multistakeholder steering committee with representation from sites, industry partners, patient advocates, and a member from the FDA (non-voting with respect to steering committee matters). The multistakeholder and site-driven approach to registry design and execution was highly efficient and resulted in the first patient enrolled within 6 months of concept development.

Conclusions: By ensuring regulatory compliant implementation of the registry, we created both a source of real-world data and a multisite platform for the conduct of future clinical trials that can be submitted to regulatory authorities to support inclusion of pediatric data in approved drug labeling. A highly collaborative approach with broad stakeholder engagement at all stages of the registry development was key to our operational success.

Keywords

Migraine; Real-World Data; Clinical Registry; Regulatory Submission

Introduction

Migraine is common in children and adolescents. By age 10, approximately 5% of children in the United States are diagnosed with migraine, and prevalence increases throughout adolescence.¹ Migraine is the 6th most disabling disease globally among 10-14-year-olds and the 5th most disabling disease globally among 15-19-year-olds.² In addition to causing significant pain, migraine causes children and adolescents to miss school, negatively affects school performance, leads to high health care costs for affected families, and has profound economic impact.³

Evidence-based therapy for migraine prevention and treatment in children remains limited.^{4,5} Recently developed novel therapeutics, including drugs, biologics, and neuromodulation devices, are safe and well-tolerated in adults.⁶⁻¹³ Pediatric studies are now getting underway to meet regulatory requirements. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require pediatric studies in order to assess safety, pharmacokinetics, and efficacy in children.^{14,15} To successfully execute multiple regulatory compliant efficacy trials conducted by different sponsors over a potentially short time span, a robust pediatric site infrastructure and innovative strategies will be needed. Current pediatric infrastructure is primarily based on the recently completed Children and Adolescent Migraine Prevention (CHAMP) Study and includes 36 U.S. sites, a clinical coordinating center, and a data coordinating center, all with extensive experience in the conduct of phase 3 clinical trials in children with migraines.^{16,17} However, existing infrastructure was not designed to take advantage of regulatory innovations aimed at

accelerating drug approvals. One promising innovation in pediatric drug development is the use of real-world data. As highlighted in the recently released Framework for FDA's Real-World Evidence Program, appropriately collected real-world data can support drug development through several key steps.¹⁸

To both leverage the opportunities of real-world data and strengthen research infrastructure, we created a regulatory-compliant multicenter prospective clinical registry of children and adolescents with migraine. The value of this registry includes (1) generating regulatory-compliant real-world data to support cross-sponsor pre-protocol collaborations, inform protocol development including patient phenotypes and site-based practice differences, assess feasibility of study design, and support FDA submissions; and (2) creating a multisite infrastructure capable of providing hands-on site training and site-to-site support, and of efficiently executing regulatory compliant prospective trials in children with migraine.

Overview and Funding

The Pediatric Migraine Registry was established with funding from the FDA (award U01FD004858; co-principal investigators [PIs] Benjamin and Cohen-Wolkowicz). This award was granted to the Duke Clinical Research Institute (DCRI) to support an overarching goal of establishing a novel, sustainable clinical trials network and combining it with state-of-the-art science to advance the availability of therapeutics and devices to children. Under this grant mechanism, we chose (among other projects) to develop and implement a regulatory-compliant real-world data registry, and use it as a mechanism to help train sites and strengthen their experience, capacity, and regulatory capability in trial conduct, while concurrently addressing the need for a national registry of real-world data of sufficient quality to support regulatory compliant pediatric migraine drug development. We acknowledge that other mechanisms may be of value to migraine drug development, including the conduct of pragmatic or direct-to-families clinical trials, but we selected the registry mechanism to provide—in our assessment—the most robust and versatile infrastructure.

Registry Development Steps

We took a stepwise, multidisciplinary, highly collaborative, and goal-oriented approach to create a robust multisite Pediatric Migraine Registry. Our goal at the DCRI was to serve as facilitators of efficient clinical study operations while providing an opportunity for site-based therapeutic area experts to drive the content and scientific mission of the registry. The project progressed from concept development (prior to protocol development) to first participant enrolled in approximately 6 months (Figure 1).

Why we selected pediatric migraine as a critical therapeutic area of need

Based on review of published peer-reviewed literature and recent FDA drug approvals, we identified migraine as one of the top therapeutic areas to have limited pediatric therapeutic labeling success despite recent legislative efforts.¹⁹ We identified several factors that may have contributed to the paucity of FDA-labeled treatment options for children with migraine (Table 1). In evaluating potential strategies to address each factor, we concluded that a real-

world data prospective clinical registry would be ideally suited to implement both immediate and longer-term solutions for pediatric migraine therapeutic development (Table 2).²⁰

Thought leadership and subject matter expertise

Because the immediate study team at the DCRI did not include experts in pediatric migraine, we reviewed the field of pediatric migraine clinical research to identify thought leaders. The team systematically searched the U.S. National Institutes of Health's (NIH's) PubMed, [Clinicaltrials.gov](https://clinicaltrials.gov), and NIH Reporter to identify investigators with a history of NIH funding, peer-reviewed publications, and leadership or participation in pediatric migraine clinical trials. Members of the DCRI team scheduled individual phone calls with 10 thought leaders who responded to an initial e-mail outreach to confirm the scientific feasibility and relevance of the proposed registry, and gauge both their interest in participation and their perception of the need for and value of a prospective registry to support pediatric migraine drug development. The perceived value of the project and overall level of interest expressed by the majority of interviewed thought leaders were the key factors in a 'go' decision to proceed with registry funding and development.

Publicizing study among potential sites

Following thought leader and subject matter expert endorsement of the unmet need for this research, we turned our attention to identifying potential sites to execute the registry. Our general approach to site selection was to include both experienced research sites and sites in rural and medically underserved areas traditionally excluded from clinical trials, to strengthen existing infrastructure while increasing the reach of a network of research-ready sites in this therapeutic area. To identify research-experienced sites, we contacted 38 site PIs of the CHAMP trial, an NIH-funded multicenter, randomized, placebo-controlled interventional trial of migraine therapeutics in children 8-17 years of age via e-mail.¹⁷ We conducted individual phone calls with the 14 CHAMP site PIs who responded to our initial e-mail outreach to confirm their interest in participation prior to formal site selection activities (see below). To identify research sites in underserved locations, we partnered with the NIH-funded Institutional Development Award (IDeA) States Pediatric Clinical Trials Network.²¹ The purpose of this network is to build research capacity within states with historically lower research participation and NIH funding, and provide opportunities for children living in these states to participate in clinical trials. With support from the IDeA States Coordinating Center, we identified 8 interested sites. Our target of 20 participating sites was chosen to provide robust infrastructure while staying within the confines of the available funding and ensuring ample opportunity for sites' input and participation in development and conduct of the registry.

Protocol development

We used an iterative and team science approach to protocol development. As a first step, we developed a protocol synopsis that incorporated initial feedback from site-based therapeutic area experts. In parallel we developed draft electronic case report forms (eCRFs) and distributed the protocol synopsis and draft eCRFs to PIs and study coordinators at preselected sites to gather preliminary input. We then invited all study personnel at participating sites to attend 1 of 2 teleconferences hosted by the DCRI. During these

teleconferences, we sought feedback on the overall design of the registry, including the number of participants, the frequency of visits, the data collected, and the forthcoming relationship between the coordinating center and the study site staff.

Following the 2 teleconferences, we incorporated the feedback and suggestions we received on the calls and developed a full protocol. Once the full protocol was completed, we distributed it to all site PIs and study coordinators for their feedback and approval.

Data collection forms and nomenclature

To ensure compatibility of data collected in our registry with other completed or ongoing pediatric migraine studies, we created our eCRFs based on the Headache Common Data Elements Version 2 developed by the National Institute of Neurological Disorders and Stroke (NINDS). We sought feedback on draft eCRFs from thought leaders and site study personnel. We especially focused on harmonizing eCRF content with assessments performed per routine clinical practice.

Site selection

A total of 22 sites expressed initial interest in participating in the registry, including 8 IDEa States network sites, and these sites were further systematically evaluated for participation. Per DCRI standard operating procedures (SOPs), our team conducted site qualification phone calls with any site (a) who had not been visited by the DCRI within the last year and/or (b) whose performance had any aberrations or prior quality concerns to clarify any extenuating circumstances that led to those concerns, as well as any steps that the sites had taken or planned to take to remediate those concerns. Following these phone calls, a total of 2 sites underwent additional remote site selection visits for more comprehensive evaluation as per DCRI SOPs. These remote site selection visits entailed the study team inquiring about the potential site's facilities, prior experience in similar trials, any ongoing competing trials, and project enrollment rates. Experience and restrictions with contracting and central institutional review board partnership were also discussed. Both qualification calls and remote site selection visits allowed for further in-depth conversation about the requirements and expectations of the study. Following completion of these visits, we selected 20 sites for initial participation in the registry. Once selected, all sites participated in an investigator meeting. A total of 3 investigator meetings were performed, all via teleconferencing. We recorded one of the initial investigator meeting presentations and made it available to sites for review on their own time prior to the third, site-wide meeting. To increase participation of sites, we asked all participants for this site-wide investigator meeting to review the recording prior to attending the meeting, and focused the meeting on the presentation of key study highlights and question-and-answer sessions. To stimulate discussion, we used the interactive question-and-answer feature of our teleconference tool to directly ask sites to answer multiple-choice questions evaluating their understanding of key study concepts. Individual contracts were executed between participating sites and DCRI in its role as the coordinating center for the registry to provide both site startup payments and milestone-based payments for subjects enrolled. Institutional review board approval was obtained by DCRI (in its role as coordinating center) and all participating sites with the option of using either local or central (WIRB-Copernicus) institutional review board services.

Patient/parent engagement

To best serve the patient community and take into account the needs of children and their caregivers, we elicited the support of DCRI's Stakeholder Engagement Group and the Research Together program. This group provides thought leadership on the science of engagement of all research stakeholders, including patients and families.^{22,23} The group provided input on the protocol draft including frequency of study visits and number of questions asked at each visit, and assisted in the development of consent and assent forms. In parallel, we reached out to the International Children's Advisory Network (iCAN), a worldwide consortium of children's advisory groups dedicated to providing children and families with a voice in medicine, research, and innovation. Both groups facilitated introduction to Miles for Migraine, a registered 501(c)(3) nonprofit organization with the mission of improving the lives of those with migraine and their families, raising public awareness about headache disorders, and helping fund a cure for migraine. The organization provided further input on how to engage children with migraine, how to seek their input on the study, and other mechanisms of interacting with this patient population.

Other stakeholder engagement

Throughout the registry development process, we continuously engaged with other stakeholders in the field. This included the NINDS, industry sponsors developing migraine therapeutics, the FDA Division of Pediatric and Maternal Health and Division of Neurology Products, both within the Center for Drug Evaluation and Research, and the American Registry for Migraine Research (ARMR) managed by the nonprofit American Migraine Foundation.²⁴ While ARMR is a registry reserved for participants age 18 years and older, we identified several areas for potential collaboration, including overlap in the collection of key data elements to simplify future joint data analyses, and developing a process to help guide migraine patients aging out of our registry into ARMR.

Steering committee and registry governance

After site selection but prior to protocol finalization, we elected a steering committee to oversee the registry. We asked all participating sites to nominate 3 representatives for membership to the steering committee, and one representative to serve as overall registry PI and committee chair. The highest vote recipients were selected for membership (Szperka, Children's Hospital of Philadelphia; Pezzuto, Nemours) and registry PI and committee co-chair (Gelfand, University of California San Francisco). We also designated steering committee positions for a patient/parent advocate (Kessel), an industry representative, a coordinating center PI and committee co-chair (Hornik), and a non-voting member of the FDA (Alexander). Per the registry governance charter, the committee is responsible for overseeing all study activities performed under the registry, and will review proposals for data analysis, any publications resulting from registry data, and any potential future collaborations or expansion of the registry. Steering committee decisions are approved by simple majority voting (with the exception of the FDA member). At the time of this writing, the composition of an external advisory board, which will support the steering committee, is being finalized. The anticipated role of the external advisory board is to provide advice to the steering committee in matters broadly related to the migraine registry, including

proposals for ancillary research studies, partnerships, expansion opportunities, and presentations and publications based on registry data.

Current Registry Structure and Capabilities

Overview and objectives of the registry.

Under the current protocol, the registry is implemented at 18 sites in 15 U.S. states, including 6 IDeA network sites. Following informed consent and assent if applicable, 200 children age 4-17 years with a diagnosis of migraine with or without aura by International Classification of Headache Disorders (3rd ed.) criteria²⁵ will be enrolled and followed at 3-month intervals for a period of up to 12 months. Importantly, participants will be asked to consent to being re-contacted for potential future trial participation, and all efforts will be made to maintain up-to-date contact information for participants and their families.

In addition to a comprehensive migraine and medical history, including use of and response to therapeutic intervention, results of neurologic examinations, laboratory assessments, and electrocardiograms performed per standard of care will be recorded. Participants will also be asked to complete the Pediatric Migraine Disability Assessment (PedMIDAS) disability scale.²⁶

Data management.

All registry data will be captured in a 21 CFR Part 11–compliant web-based data entry system hosted and supported by the DCRI (IBM Clinical), where the data will be stored. Site personnel are responsible for completeness and accuracy of data entered into eCRFs, which are guided by comprehensive eCRF instructions and formal site training, and monitored according to a data monitoring plan that includes both automated and manual queries, source document verification when needed, and a complete audit trail recorded by the electronic data capture. Quality assurance and quality control activities are performed throughout the data lifecycle to verify project compliance with DCRI SOPs. All site personnel involved in the conduct of the registry, including data entry, are required to document adequate training on the registry protocol and in general conduct of clinical research including human subject protection and good clinical practice. Overall, the data management policies of the registry are designed to mirror those required in a clinical trial conducted under investigational new drug application, to allow regulatory submission of the registry data and support site data management infrastructure for future clinical trials. Data entry, storage, and confidentiality matters are comprehensively described in the registry protocol and the informed consent form as applicable.

Monitoring activities are outlined in a registry Clinical Monitoring Plan and follow DCRI SOPs. Monitoring is done through combined remote and on-site monitoring. The latter is reserved for sites with increased database queries, accelerated enrollment rates, or any data or study concerns noted by the DCRI study team. In addition to monitoring, site training visits will be performed as needed.

To further augment the capabilities of the registry, we partnered with vendors to support 3 key registry features (Figure 2):

Biorepository capabilities are provided by OpAns LLC (Durham, NC), a full service and accredited bioanalytical laboratory. Registry participants will be asked to provide biological specimens, including blood, urine, saliva, and stool, via opt-out consenting. Specimens will be stored at OpAns for future analysis, including potential genetic analysis under full HIPAA compliance. In addition to providing a biorepository of children with migraine, the biorepository capabilities will be used to train and assist sites in developing their biological sampling and handling capabilities for future studies.

Patient-reported headache diaries will be kept by participants, who will be provided with a research version of the commercially available MigrnX mobile application developed by SensorRx (Charlotte, NC). This tool was initially developed to facilitate clinical care of adults with migraine. The clinical version was adapted for use in pediatric research studies with input from pediatric headache specialists. MigrnX was selected by the steering committee based on its history of use in this population and a demonstration of its capabilities. Using this app, participants will provide information about migraine attacks in real-time format. They will also be able to enter daily headache diary data; hence, this app can be used to collect data for both acute and preventive migraine treatment trials. Data entered by participants will be automatically pushed from SensorRX servers to our registry database. This will allow comprehensive evaluation of patient-reported data to complement information collected during study visits.

Site data visualization and benchmarking will be performed using Remarque Systems (Chapel Hill, NC). This customizable platform is fully compatible with the registry's electronic data capture, and will provide data aggregation and analytics to support trial oversight and risk processing. Both the coordinating center and participating sites will have access to a cloud-based interface to review registry enrollment, data quality, and data trends. Sites will be able to benchmark in real time against other registry participants, while the coordinating center will have the ability to identify site and registry-wide data trends in real time, and perform head-to-head comparisons between all participating sites. Sites may use the data visualization data at their discretion for activities outside of the scope of this registry.

Future Directions

To date, the registry has enrolled 46 participants. In parallel with the continued enrollment and follow-up of participants, several additional activities are underway, including evaluation of international expansion as well as rollout of a site-to-site mentorship program.

International expansion

We are in the process of planning an international expansion to European countries and Canada. We are leveraging our partnership with the Maternal Infant Child Youth Research Network in Canada and the Connect 4 Children Initiative in Europe to discuss regulatory and operational approaches to expand the registry. To operationalize this global effort, we are also evaluating partnership with global commercial research organizations, whose bandwidth and capabilities are best suited to perform this type of work.

Site-to-site mentorship program

We are in the early stages of implementing our site-to-site mentorship program. Under this program, research-experienced sites with a self-identified interest will be partnered with sites with less experience to provide direct, peer-to-peer mentoring and support. The DCRI will continue to monitor all aspects of study participation and provide guidance in its role as the coordinating center. However, we hypothesize that the site-to-site mentoring will more efficiently address several practical concerns that less experienced sites may have regarding study execution. To date, we have identified several sites interested in serving as mentors. As the program gets underway, we will oversee its implementation, track interaction types between sites, and review overall performance and the value of the program to study execution. We anticipate that this program will contribute toward strengthening the overall pediatric research infrastructure at participating sites.

Opportunities for ancillary studies

The infrastructure created by the registry provides an opportunity to conduct prospective and retrospective observational and interventional studies in children with migraine. We continue to encourage participating sites to explore how the registry may support investigator-initiated or sponsored research efforts. Proposals for additional research are reviewed and approved by the steering committee prior to implementation. Any proposals that have the potential to improve the health and wellbeing of children or adolescents with migraine will be considered. To date, 2 proposals for extramural funding have been submitted by registry investigators and are undergoing review and evaluation.

Long-term sustainability

To maximize the public health benefit and meaningfully improve pediatric migraine drug development, long-term sustainability of the registry is essential. We will implement a multipronged approach in an attempt to secure funding necessary to increase enrollment numbers, lengthen follow-up, and expand the capabilities of the registries including implementing pragmatic and direct-to-families elements. Ideally, a variety of funding sources from government, foundations, and industry will support these future efforts. To date, we are conducting outreach campaigns with industry, informing them of the capabilities of the registry and gauging their interest in partnership based on the needs for their drug development programs. We have also actively encouraged and supported applications for government and foundation funding that would support the registry while simultaneously leveraging its capabilities to efficiently and rigorously address clinical and scientific issues. Mirroring the registry development process, we will conduct these outreach efforts using a collaborative approach with broad stakeholder engagement under the guidance of our external advisory board.

Conclusions

In summary, we developed a multisite, multistakeholder, prospective, real-world data registry of children and adolescents with migraine. By ensuring regulatory-compliant implementation of the registry, we created both a source of real-world data and a platform for the conduct of future clinical trials that can be submitted to regulatory authorities to

support inclusion of pediatric data in approved labeling of therapeutics. A highly collaborative approach with broad stakeholder engagement at all stages of the registry development was key to our operational success.

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Pediatric Migraine Registry sites, principal investigators, and study coordinators

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Abbreviations:

DCRI	Duke Clinical Research Institute
eCRFs	electronic case report forms
NINDS	National Institute of Neurological Disorders and Stroke

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Figure 1.

Registry Development Timeline

eCRF, electronic case report form; EDC, electronic data capture; ICF, informed consent form; IRB, institutional review board.

Figure 2.
Registry Organization Chart

Table 1.

Select challenges and potential solutions to development of drugs or other therapeutics for children and adolescents with migraine

Select Challenges	Potential Solutions
<ul style="list-style-type: none">• Efficacy extrapolation from adults not possible	<ul style="list-style-type: none">• Robust, regulatory compliant infrastructure• Biomarkers as efficacy surrogates• Improved methods for collection of patient reported outcomes
<ul style="list-style-type: none">• High placebo response rate and other patient characteristics may contribute to trial failures	<ul style="list-style-type: none">• Natural history• Cohort enrichment
<ul style="list-style-type: none">• Multiple drugs and therapeutics from competing sponsors in adult development	<ul style="list-style-type: none">• Rapid enrollment at trial ready sites• Master protocols

Table 2.

Solution implementation via real-world registry

Therapeutic Development Solution	Implementation of Solution within a Registry
• Robust trial infrastructure	<ul style="list-style-type: none"> • 20 U.S. sites with collaborative experience enrolling children with migraine under regulatory compliance • Site-to-site mentorship program and real-time feedback report
• Biomarker validation	• Biospecimen (blood, urine, other) sampling and correlation of biomarker (including genetic) with clinical signs and symptoms
• Improved facility for collecting patient-reported outcomes	• Customizable, commercial, mobile app with data collection integrated into 21 CFR Part 11–compliant database
• Natural history and cohort enrichment	• Longitudinal data collection in 200 children
• Rapid enrollment	• Contact information and consent for re-contacting
• Master protocol	• Site and coordinating center infrastructure to develop and implement a multitherapy master protocol ⁷