Pediatric Migraine Registry

Prospective National Multicenter Registry of Children 4 to 17 Years of Age

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Overview

- Utility of registry in drug development
- Registry structure and development
- “Snapshot” of current data
- Leveraging registry infrastructure to develop clinical trial endpoints

Scope of Problem: Pediatric Migraine

- Top 5 most prevalent childhood disease in United States
- $36 billion estimated annual economic impact (2001-2002)
- Chronic neurovascular disease
- Treatment is both acute and preventive

- Pediatric studies needed under Section 505B of the Federal Food Drug and Cosmetic Act (21 U.S.C.355c)
  - Partial waiver generally granted for under 6 years
- No extrapolation of efficacy
- PK trials followed by safety and efficacy
- Enrichment recommended given high placebo effect

Victor TW. Cephalagia 2010
GBD 2015. Lancet 2016
Arruda MA. Neurology 2012

RWD Registry as Drug Development Tool

Challenge	Potential Solution	Implementation via Registry
• Extrapolation of Efficacy not Permitted	• Robust regulatory compliant clinical trial infrastructure • Efficacy surrogates • PROs	• 20 US sites enrolling regulatory compliant • Biobanking • Customizable mobile app integrated with database
• High placebo response rate	• Natural history • Cohort enrichment	• Longitudinal RWD collection in 200 children
• Multiple therapeutics under development	• Rapid enrollment at trial ready sites • Master Protocols	• Contact information and consent for re-contact

Objectives

- **Primary Objectives**
  - Prospectively collect regulatory compliant data from children and adolescents with migraine to inform future clinical trials
- **Exploratory Objectives**
  - Characterize utilization of therapeutic interventions in children and adolescents with migraine
  - Evaluate history and clinical course of children and adolescents with migraine
  - Evaluate genetics and biomarker profiles of children and adolescents with migraine

Registry study design

- Prospective enrollment of **200** participants across **20** US sites
- Inclusion:
  - 4 to 17 years of age inclusive at the time of enrollment visit
  - Meets International Classification of Headache Disorders, 3rd edition criteria for migraine with or without aura
  - Guardian provides informed consent/HIPAA
  - Participant provides assent if developmentally appropriate and required by the institutional review board
- Exclusion:
  - Any condition which would make the participant, in the opinion of the investigator, unsuitable for the study

Hornik et al., Headache; *in press*

Procedures

	First Visit Month 0	Subsequent Visit #1 Month3 (+/-45 days)	Subsequent Visit #2 Month6 (+/-45 days)	Subsequent Visit #3 Month9 (+/-45 days)	Subsequent Visit #4 Month12 (+/-45 days)
PROCEDURE					
Informed consent/assent	X				
Demographics	X				
Contact information	X	X	X	X	X
Medical and migraine history • Medical history • Migraine and headache questionnaire • Concurrent medications • Migraine history • Migraine triggers • Migraine symptoms • Migraine therapeutics	X	X	X	X	X
Neurologic examination	X	X	X	X	X
Laboratory evaluations	X	X	X	X	X
Height and weight	X	X	X	X	X
Electrocardiogram	X	X	X	X	X
Biological specimen samples for biobanking	X	X	X	X	X
PedMIDAS	X	X	X	X	X
Reminder to complete patient reported data via mobile app	X	X	X	X	X

Registry Features

- Coordinating center with regulatory clinical trials experience:
  - 21 CFR part-11 compliant EDC
  - Remote and in-person data monitoring
- Biobanking capabilities
- Patient-reported outcomes via mobile device application:
  - MigrnX by SensorRX
- Opt-out re-contact
- Site feedback report
- Site-to-site mentoring program

Leadership and Oversight

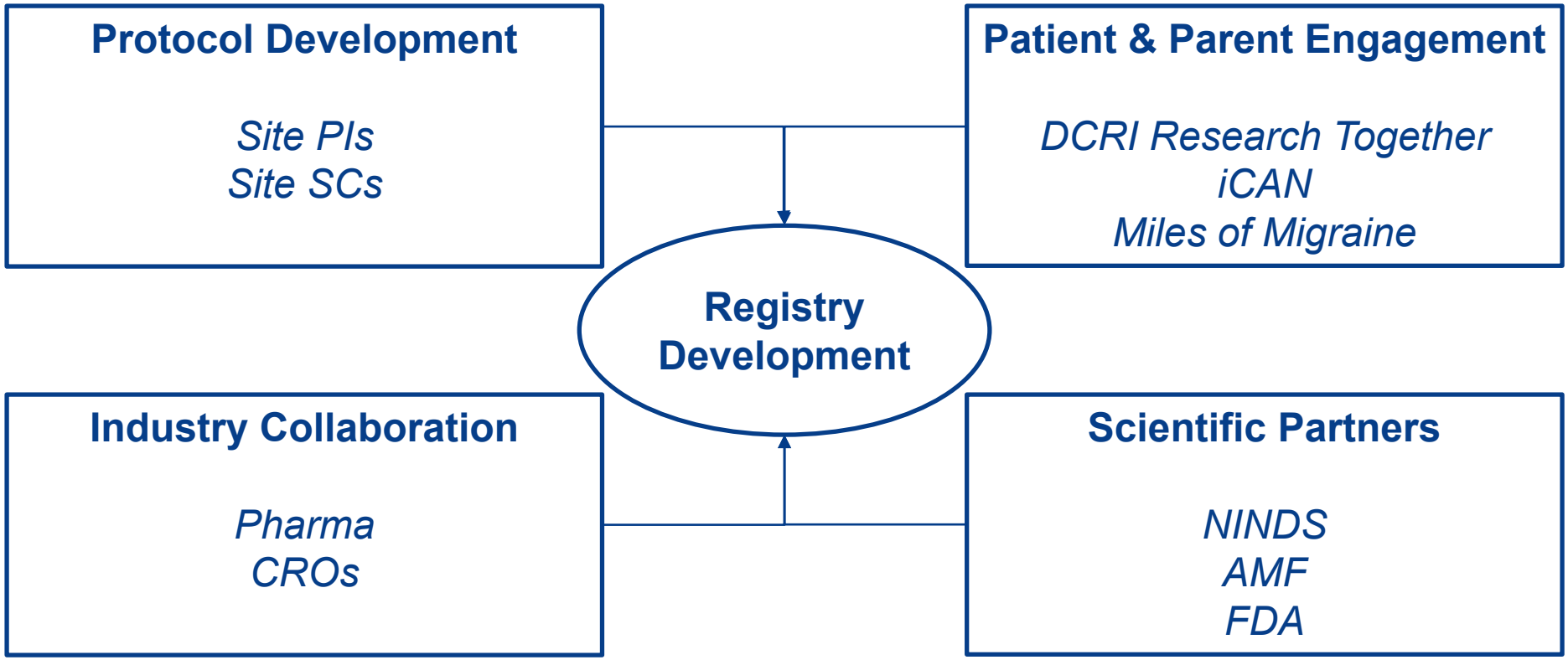
Steering Committee

- Amy Gelfand, UCSF; PI/Co-Chair
- Christoph Hornik, DCRI CC-PI/Co-Chair
- Christina Szperka, University of Pennsylvania
- Tara Pezzuto, Nemours AI DuPont Hospital for Children
- Shirley Kessel, Miles for Migraine
- John Alexander, FDA (non-voting)
- *Industry*

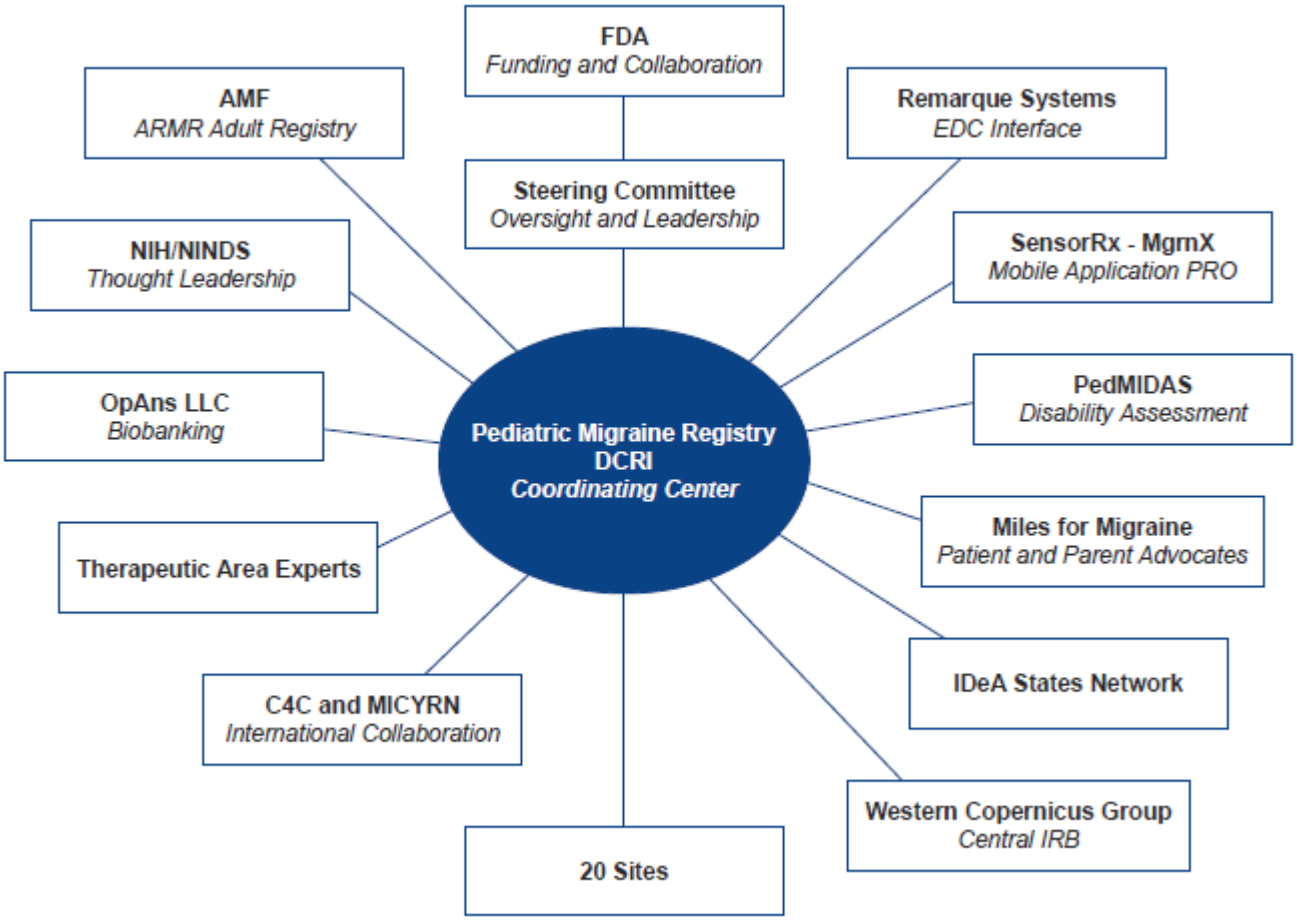
External Advisory Board

- Andrew Hershey, Cincinnati Children's Hospital
- Amy Brin, Child Neurology Foundation
- Marcy Yonker, Children's Hospital Colorado

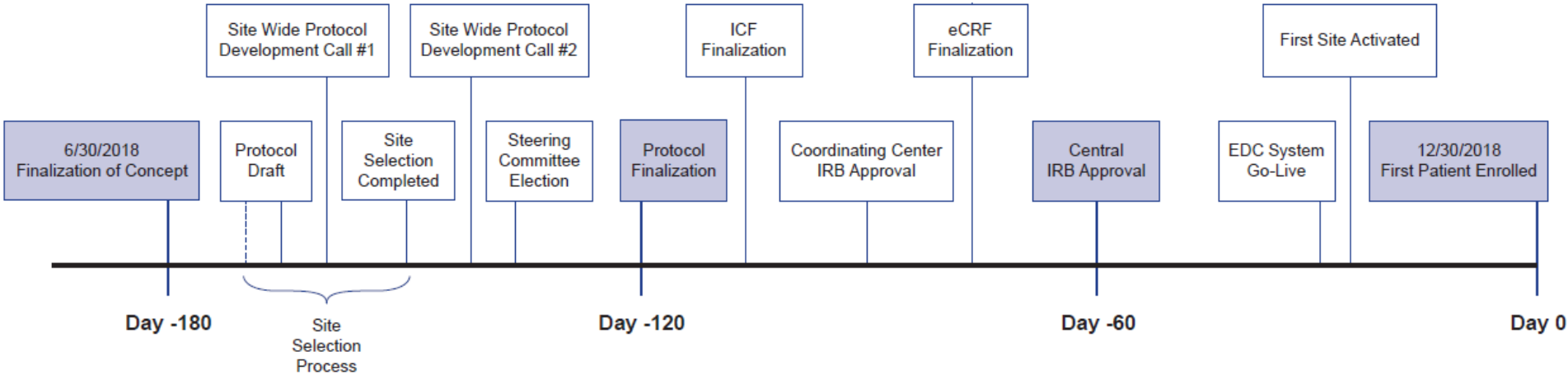
Team Science



Collaborations



Timeline


Site Wide Protocol Development Call #1
Site Wide Protocol Development Call #2
ICF Finalization
eCRF Finalization
First Site Activated
6/30/2018 Finalization of Concept
Protocol Draft
Site Selection Completed
Steering Committee Election
Protocol Finalization
Coordinating Center IRB Approval
Central IRB Approval
EDC System Go-Live
12/30/2018 First Patient Enrolled
Day -180
Site Selection Process
Day -120
Day -60
Day 0

Current Data Snapshot

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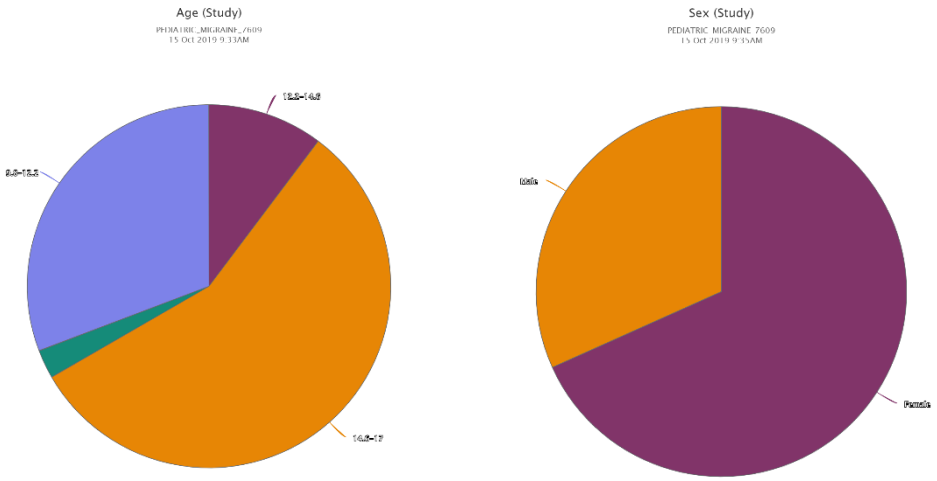
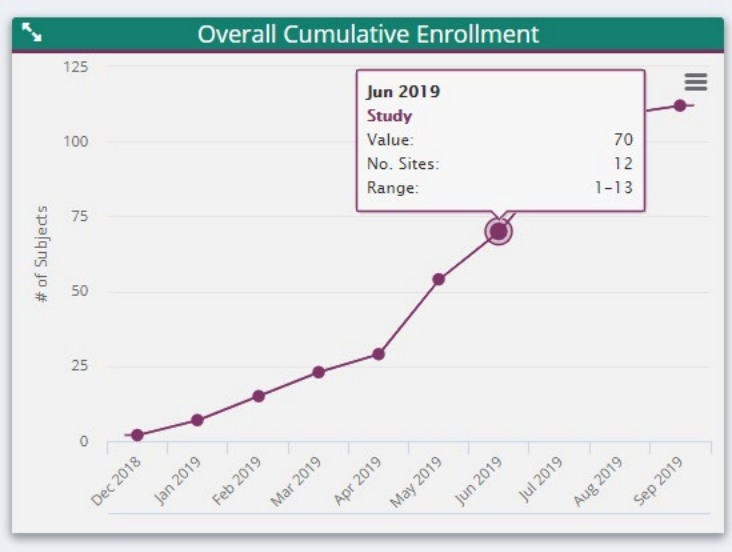
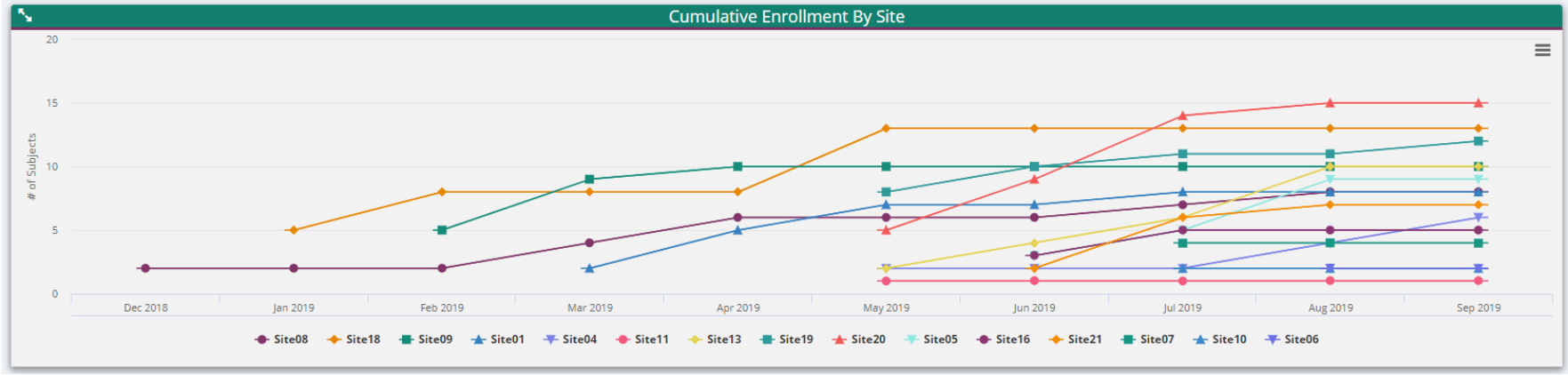
TO CLINICAL PRACTICE

Enrollment and Demographics N=144

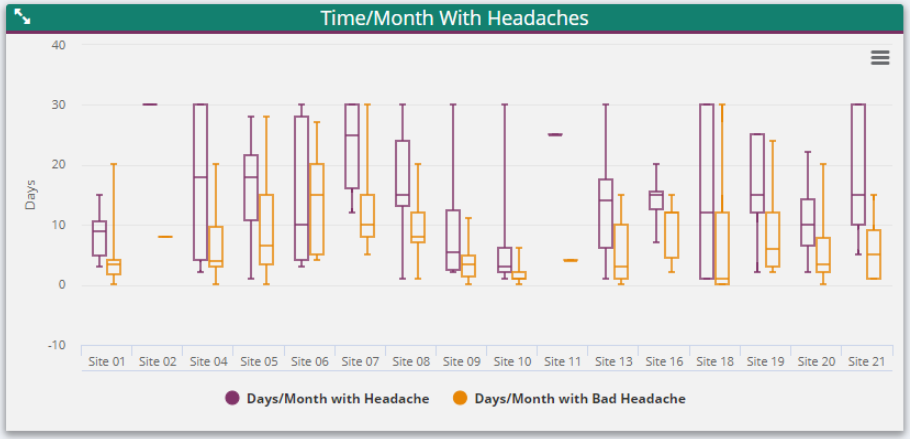


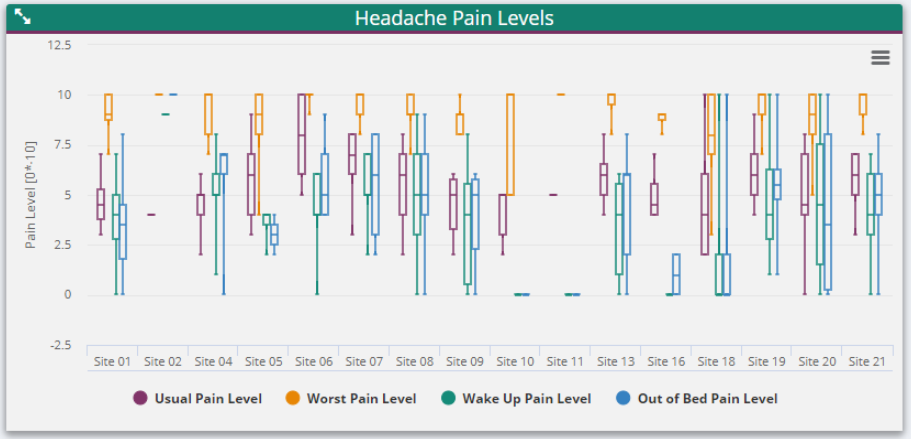


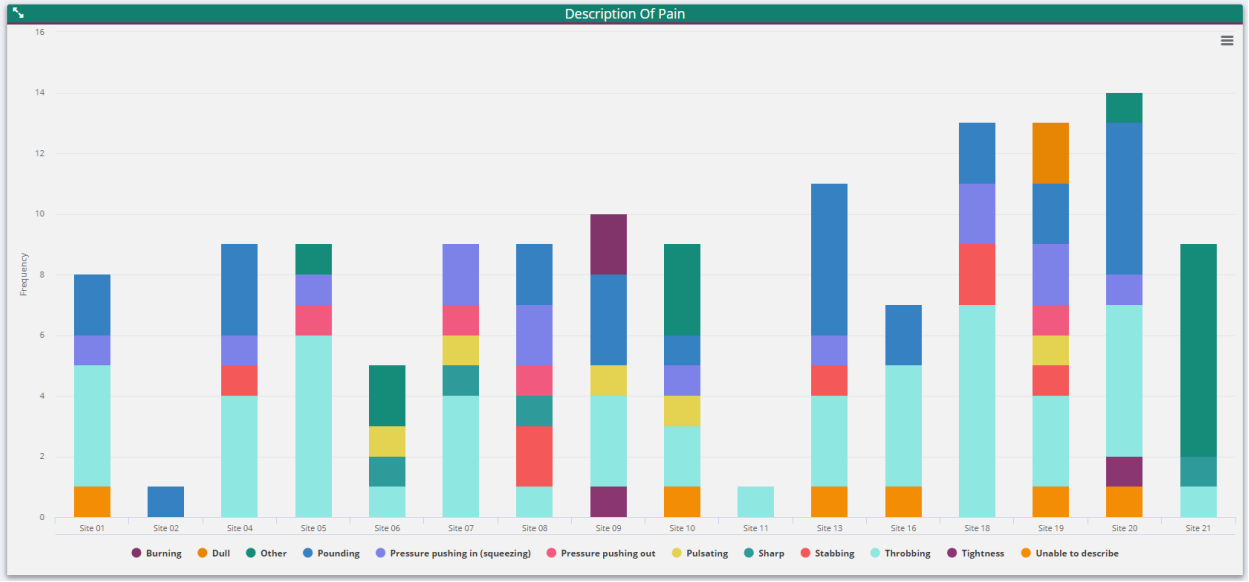


https://remarquehub.com/organization/18/study

Headache Characteristics







Endpoint Development

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TO CLINICAL PRACTICE

Migraine Trial Endpoints

- FDA Guidance for Acute Treatment:
  - Effect on co-primary endpoints: pain; nausea; photophobia; phonophobia
  - Effect on pain (at 2 hrs) + most bothersome symptom
  - Measured by patient self-reporting using 4-point Likert scale

- Preventive therapies
  - Days with / with severe migraine
  - Days missed school
  - Migraine related disability questionnaires (PEDMIDAS)

US FDA Guidance for Industry. 2018
EMA 2007

Patient Reported Outcomes

- Home-Based Trial of Melatonin vs. Placebo (NCT02344316)
- N=31 participants; randomized 1:1 to melatonin (3mg) vs. placebo

Recruitment Method	N=31
Clinic	6
Newspaper & social media advertising	14
EMR letter invitation & other	11

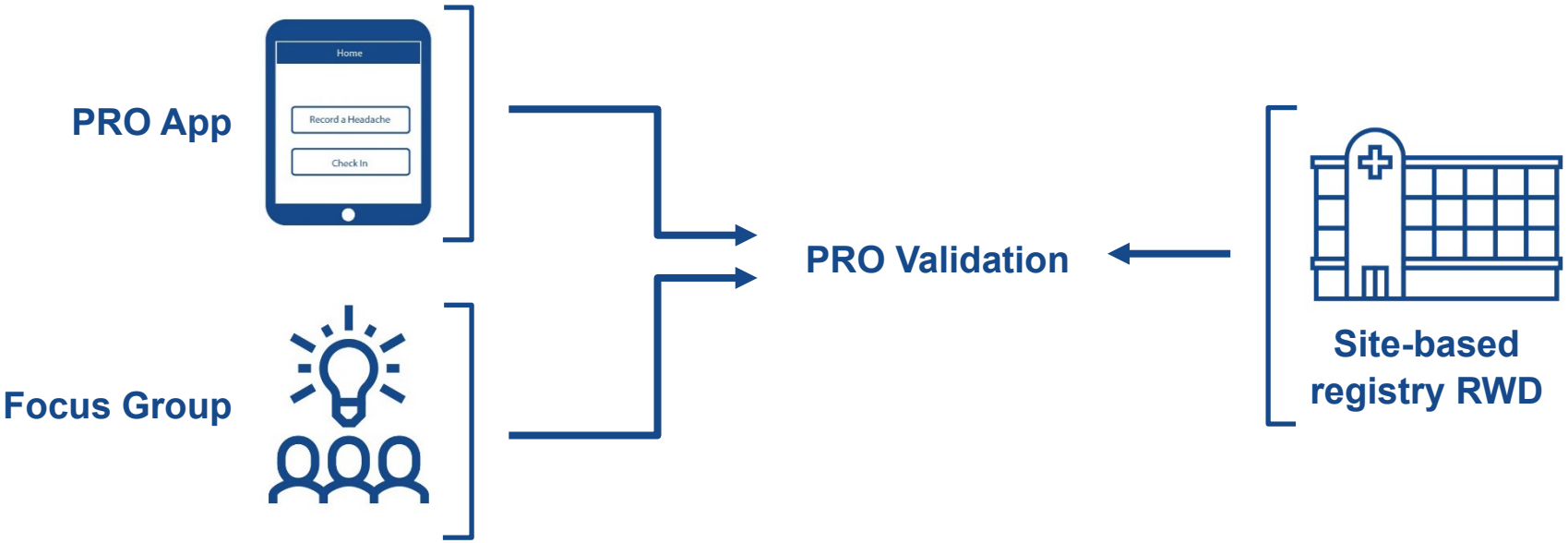
- Study screening website + single clinic visit for consenting
- Daily migraine diary completion (>80%) with text-message based reminder
- Fitbits for sleep recording
- Telephone assessment of adverse events

Gelfand AA. JAMA Neurol. 2017

Patient-generated RWD to inform trials

Deliverable: validation report of patient-reported vs. site-based data

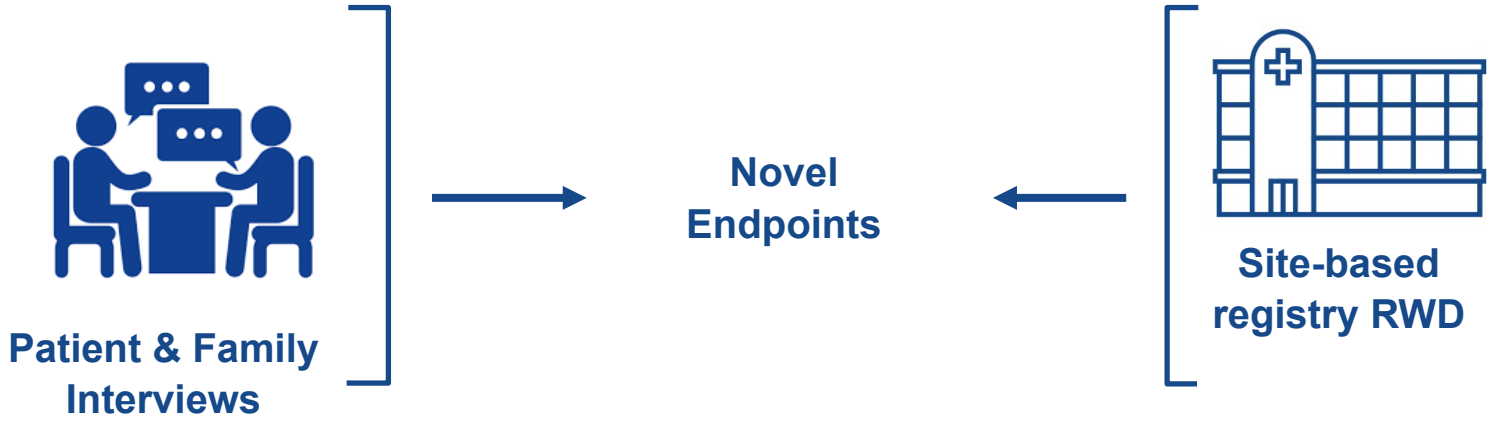
A patient-centric approach to collect and validate end-point data



Patient/Family defined endpoints

Deliverable: qualitative and quantitative analysis of patient/family perception of migraine and clinical trial endpoints.

A patient-centric approach to develop end-point data



Conclusions

- Government funded registry to advance pediatric drug development
- Developed through team science and highly collaborative approach
- Infrastructure for future research:
  - Endpoint development and validation
  - RWD reports
  - Master protocol design and execution

Funding Sources & Acknowledgements

- FDA Office of Pediatric Therapeutics
  - 1U18FD006298-01 (PI Cohen-Wolkowiez, Benjamin)
- Burroughs Wellcome Fund
  - IRSA 1020016 (PI Hornik)
- FDA OPT
  - Carrie Bryant
  - Suzie McCune
  - Gerri Baer
  - John Alexander
- DCRI
  - Rachel Olson
  - Alex Hammett
  - Mark Ward
- Site PIs and Staff
- Participating Families

Sites

Site	Principal Investigator(s)	Study Coordinator(s)
Akron Children's	Victorio	Pownhall, Morgan, Ekers
Cleveland Clinic	Rothner	Carabello
CHOP	Szperka	dePrado
Cinicinnati Children's	Hershey	
Children's Mercy	Bickel	Boorigie
UCSF	Gelfand, Irwin	Saeed
Colorado Springs	Kutz	Ventimiglia
Michigan Head Pain	Saper	Gruber
Nicklaus Children's	Hagler	Diaz, Quintero
Nebraska	Rathore	Aikman
Oklahoma Health Sciences	Guthrie	Chandler
Rhode Island Hospital	Kerman	Ryan
Seattle Children's	Blume	Lee-Eng
St. Louis University	Arun	Stieglitz
University of Maryland	Gladstein	Brengle
Texas Children's	Patnyiot	
Nemours	Ross	Roach
University of Louisville	Doll	Thomas
USC Columbia	Turley, Nahouraii	Adams
University of Vermont	Hirtz	McHale

BACKUP SLIDES

Steering Committee

- Composition:
  - Amy Gelfand MD, UCSF; PI/Co-Chair
  - Christoph Hornik MD PhD MPH; CC-PI/Co-Chair
  - Christina Szperka MD MSCE, University of Pennsylvania
  - Tara Pezzuto DNP, Nemours AI DuPont Hospital for Children
  - Shirley Kessel, Miles for Migraine
  - John Alexander MD, FDA (non-voting)
  - *Industry*
- Nomination process for membership & co-chairs among all site PIs
- Broad scientific oversight, data sharing, access and publication

External Advisory Board

- Andrew Hershey, MD, PhD, FAHS. Cincinnati Children's Hospital
- Amy Brin, CEO Child Neurology Foundation
- Marcy Yonker, MD. Children's Hospital Colorado
- Nominated by Steering Committee
- Scientific input

Protocol Development

- Obtained input from potential site PIs & SCs
  - Site wide protocol development calls
  - Review & written feedback
  - PI and SC sign-off on final draft
- DCRI Data Management & Data Solutions groups
- Protocol shared with NIH and FDA for input

Patient/Parent Engagement

- Identify patient advocate through DCRI Research Together
  - Questionnaire to determine prior involvement and advocacy, willingness to engage with study team
  - Statement of Work to outline expectations

- Pediatric migraine advocacy groups: Miles for Migraine

- International Children's Advisory Network (iCAN) Research

Industry Collaboration

Pharma

- Targeted outreach
- SC membership opportunity
- Input into registry procedures to support drug development
  - Stool specimen
  - Plasma sampling

CRO

- Low risk collaborative opportunity
- Complementary capabilities
  - EDC features
  - Laboratory services

Scientific Partners

- NINDS
  - Common data elements
  - Biobanking
  - U01 application

- American Migraine Foundation ARMR
  - Data harmonization
  - Transition when reaching age 18
  - Longitudinal data