Whitepaper:

SETTING A NEW STANDARD FOR MIGRAINE CLINICAL RESEARCH

Authors: Dr. Sonia Quintas, MD, MSc, Theresa Veira, MSN, MBA, Pora Kuperman, MPH, PhD

Migraine is classified as a highly prevalent neurological disease, affecting over 1.1 billion people worldwide and ranking as the second leading cause of disability. Migraines are not merely just a pain syndrome, but a complex neurological disorder involving altered neurophysiological states and progressive changes in brain networks. Migraine chronification *(the transition from episodic to chronic migraine, that*[1] *occurs annually in 3% of patients with episodic migraine)* is associated with progressively persistent central and peripheral nervous system sensitization, altered excitability, and maladaptive neuroplasticity. This process highlights how migraine involves trigeminovascular dysfunction, heightened sensory processing, and altered cortical inhibition.

Migraine pain is unique in the way it unfolds through distinct phases *(prodromal phase – aura phase – headache phase – postdrome phase)* that prove that migraine pain is not a single event, but a multi-stage neurological process.

Understanding both the phases and the role of triggers is essential for appreciating why migraine pain differs from other types of pain, in the way that migraine is not just a response to an external stimulus or injury, but the result of a brain that temporarily shifts into a vulnerable state.

Another defining feature of migraines is the strong relationship with triggers, which can vary widely between individuals and even within the same patient over time. These triggers do not directly cause migraine attacks in a simple way; instead, they interact with an already sensitive brain. Migraines often coexist with comorbidities such as depression, anxiety, medication overuse, and sleep disorders, which can modulate disease progression and patient response to interventions. This inherent heterogeneity affects both efficacy and safety outcomes in trials and suggests that study designs should incorporate careful phenotyping and longitudinal assessment to account for comorbidity-related influences on migraine evolution.

PROACTIVE PLACEBO EFFECT MANAGEMENT

Research indicates that over time placebo response in preventative migraine studies has increased considerably[2], while drug responses have remained stable, leading to an overall decrease in treatment effects. Furthermore, across medical conditions, placebo response is typically higher for newer medications or treatments.[3] Pursuant to this, a systematic review of preventative pharmacological migraine treatments from 2021[4] identified that 42% of trials failed to meet statistical significance of the primary endpoint. Furthermore, the analysis found that the significant differences were driven by the 60% difference in trial success between studies with less than 20% placebo response and those with greater than 30% *(Table 1)*.

TABLE 1: PLACEBO RESPONSE SUCCESS RATE

Placebo Responders	Success*
≤ 20%	100%
21-30%	50%
>30%	40%

**Success refers to adequately meeting statistical significance of the primary endpoint*

Table: relationship between placebo responders and success to meet primary endpoint according to Vollert et al (4)

It is important to note that since patient-reported outcomes are subjective, especially in pain-conditions such as migraines, placebo response is less avoidable. It is imperative that we understand any potential mitigating factors. One possible factor is the patient's ability to discern and report their own symptoms and pain[5]. In that, if a patient fails to understand the correct reporting of their pain and symptoms, they will demonstrate both higher placebo responses and reduced differences between drug and placebo.[6] If this is due to expectation bias[7], where the expectation of a therapeutic benefit activates reward mechanisms, one suggested solution would be to minimize expectations though **Placebo Response Reduction Training**[8], or use of the **Placebo-Control Reminder Script**[9] which reminds patients of the factors which may cause placebo responses. Other factors, such as the mode of administration or clinical environment, may contribute to the "contextual effect".[10] These effects mentioned provide an opportunity to adjust the impact of placebo by focusing on patient expectations as well as the interaction with provider, setting, and culture.

Language from the placebo-control reminder script is first introduced to the patient in the informed consent form. Thereafter, the same language is utilized at each patient visit or interaction to maintain a consistent and neutral approach among the patient and the clinical research team. Key components of the script include neutral tone, clarifying placebo possibility, blinding reminder, encouraging accurate reporting, and reducing bias.

By providing the same training to all study sites, Medpace works to mitigate site-specific factors which may be disproportionately causing placebo response. If the root cause, however, is inaccurate for subject reporting, methods[11] which train participants to accurately rate their pain. Another method to reduce the placebo response is to utilize a placebo run-in phase, though the efficacy of this approach is still under debate.[12] Finally, the use of a pain-rating run-in period has also been suggested in conjunction with the placebo run-in phase in order to ensure the patient's ability to comply with pain diary completion and observe their day-to-day pain variability.

Furthermore, ongoing data surveillance to proactively monitor clinical data to detect quality concerns with outliers such as inconsistent pain ratings is an additional measure to mitigate placebo response. At Medpace, our team has experience supporting the statistical evaluation of critical data to identify patients and sites exhibiting atypical data patterns. This is completed via our ClinTrak® system that aggregates large volumes of data across multiple internal and external data sources and facilitates centralized monitoring by allowing teams to visualize, interpret, and interact with the real-time study data to identify trends, outliers, and other points of interest, in supporting faster risk remediation actions and forward-looking study decisions.

REGULATORY-READY EXECUTION ACROSS MIGRAINE POPULATIONS

Like adult migraine presentation, migraine is a leading cause of disability across all age groups in children and adolescents, one that increases with age from 3% in young children, to 8-23% in adolescents.[13,14] However, clinical expression in children differs substantially from that in adults, and the differences are not merely academic: they have direct implications for diagnosis, treatment response, and inclusion in clinical trial. In terms of diagnosis, presentation is often shorter in duration, more bilateral with prominent gastrointestinal symptoms, and higher prevalence of motion sensitivity[15] and vertigo. Younger patients may struggle to describe pain quality or associated symptoms, and in this context children's drawings of headache provide a compelling window into this different clinical language.[16]

Regarding pharmacological interventions, treatment options have largely been based on adult studies, although treatments deemed effective in adults and adapted for use in children may not be efficacious. Differences in brain maturation, receptor expression, pharmacokinetics, and central pain processing suggest that efficacy and tolerability observed in adults cannot be assumed in children.[17,18,19,20] Furthermore, like their adult counterparts, young migraineurs also demonstrate a high impact of the placebo effect, with large reductions in both the frequency and intensity of migraine attacks in the placebo arm.[21,22] The International Headache Society has provided ad hoc guidelines to assist in the design and execution of clinical trials in children and adolescents with migraines. These include such suggestions as age at entry must ensure adequate age strata, and a minimum 28-day baseline period should be followed by a treatment period of at least 12-weeks.[23]

From a clinical development perspective, these differences have critical consequences as eligibility criteria based on adult migraine definitions may inadvertently exclude children with genuine migraine and endpoints and patient-reported outcomes may lack sensitivity for pediatric populations. Incorporating developmentally appropriate diagnostic tools, including visual or narrative methods, and adapting endpoints to pediatric-relevant outcomes can enhance trial validity and success.

Healthcare systems worldwide are shifting towards the patient-centered care (PCC) model[24], with the incorporation of patient-reported outcome measures (PROMs) being touted as an effective way to guide healthcare in this direction.[25,26,27] When discussing the pediatric population, it is imperative to address age-related variations in the comprehension of health concepts and the differences in age-related vocabulary. There is evidence to suggest that children above the age of eight can reliably report if PROM instruments are developed to accommodate their vocabulary as well as cognitive and reading abilities.[28,29] Generally, PCC in pediatric clinical settings, including clinical trials, include family caregivers as those who act as the primary agent in the delivery of the patient's care. With this, the evidence of agreement between pediatric self-reported and proxy-reported outcomes is considered tenuous.[30,31,32] For example, many studies have found that parents underestimate their child's pain-related functional disability.[33,34] As such, wherever possible pediatric migraine trials should include both patient and proxy PROMs to allow for the greatest depth of understanding, and likelihood of accurate reporting. For example, parents may be asked to rate their child's pain on a 0-10 NPS, while children as young as four[35] might do better if provided with the Faces Pain Scale-Revised[36] which is devised for use specifically in the pediatric population. Other outcome measures traditionally used in adult studies – such as pain freedom at two hours – may not fully capture meaningful benefit in children, whose disease burden often manifests through school absenteeism, reduced participation, or emotion distress.

KEY TRENDS FOR MIGRAINE

For many years, migraine clinical trials relied on relatively simple endpoints, such as reductions in monthly migraine or headache days, or pain intensity during attacks. While these measures remain useful, migraine complex physiopathology shows that they only partially reflect the real burden of migraine as it is now understood as a condition with cumulative effects that extend beyond individual attacks and in which the aim should be to change the course of migraine itself and not just mitigating attacks.[37] As a result, there is a growing shift toward endpoints that better capture meaningful disease control, rather than isolated symptom improvement. Sensory symptoms, disability scores, and quality-of-life measures help capture the real-world impact of migraine, and how migraine affects daily life, work, sleep, and emotional well-being.

A recent position statement from the International Headache Society proposes[38] raising the bar for what constitutes success in migraine prevention and has categorized outcomes into four tiers:

1. Migraine Freedom
2. Optimal Control
3. Modest Control
4. Insufficient Control

For example, previously a 50% reduction in monthly migraine days was the usual threshold for considering a participant as a responder, but in participants with difficult-to-treat migraine, a 30% or higher reduction is considered significant. These endpoints are easier to interpret for non-specialists or regulators and better align with the patient's expectations of restoring normal life.

Digital pain tracking tools have become a key enabler of this evolution in the way that they offer the possibility to capture the day-to-day reality of living with a migraine in real time, reducing recall bias and capturing the fluctuating nature of migraines more accurately. These tools can record not only headache occurrence, duration, associated symptoms, functional impact, medication use, and recovery patterns, providing a much more detailed picture of disease burden.

By systematically collecting high-quality patient-reported data, trials can better align with modern definitions of migraine control and prevention, allowing investigators to assess patterns such as consistency of response, residual symptoms between attacks, or early warning signs of worsening disease, while reducing reliance on memory. In this way, digital tools help bridge the gap between evolving scientific standards and practical, scalable trial execution, ensuring that endpoints remain both scientifically robust and meaningful to patients.

Advances in migraine neuroscience have reshaped how the disease is conceptualized, particularly the understanding that repeated attacks can lead to long-lasting changes in pain processing and brain excitability. Modern trials increasingly reflect the idea that migraine exists along a continuum of disease activity. This perspective encourages operational decisions that consider baseline disease stage, risk factors for progression, and the presence of interictal symptoms.

Incorporating the knowledge into trial planning supports more appropriate inclusion criteria, longer follow-up periods, and outcome measures that reflect changes in disease stability over time. Studies are now better positioned to evaluate whether treatments influence not just symptoms, but the underlying course of the disease.

CONCLUSION: A STRATEGIC CRO PARTNER FOR MIGRAINE DRUG DEVELOPMENT

As migraine research continues to evolve, so do the challenges of conducting trials, with ambitious endpoints and complex designs. Managing the high variability of migraines has become one of the central challenges in clinical research. Migraine populations are highly heterogeneous, with differences in disease severity, comorbidities, medication use, and symptom patterns. Without careful trial planning and execution, this variability can obscure true treatment effects and make results difficult to interpret.

Experience in migraine research allows CROs to bring expertise in migraine-specific trial design and patient management, helping to support consistent patient selection, standardized use of digital tracking tools, and reliable collection of patient-reported outcomes. This operational expertise helps ensure that evolving endpoints are measured accurately and consistently across study sites. By reducing noise and improving data quality, specialized CROs, like Medpace, can enhance signal detection, making it easier to distinguish real therapeutic benefits from background variability.

Tackle complex and challenging diseases with our highly experienced in-house neurologists that are embedded throughout every study. Our neuroscience physicians have expertise in pain clinical development and provide strategic direction for study design and planning, train operational staff, work with investigators, provide medical monitoring, and are available to meet with regulatory agencies if the Sponsor desires.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

REFERENCES

1. Torres-Ferrús M, Ursitti F, Alpuente A, Brunello F, Chiappino D, de Vries T, Di Marco S, Ferlisi S, Guerritore L, Gonzalez-Garcia N, Gonzalez-Martinez A, Khutorov D, Kritsilis M, Kyrou A, Makeeva T, Minguez-Olaondo A, Pilati L, Serrien A, Tsurkalenko O, Van den Abbeele D, van Hoogstraten WS, Lampl C; School of Advanced Studies of European Headache Federation (EHF-SAS). From transformation to chronification of migraine: pathophysiological and clinical aspects. J Headache Pain. 2020 Apr 29;21(1):42. doi: 10.1186/s10194-020-01111-8. PMID: 32349653; PMCID: PMC7189559.

2. The temporal trend of placebo response in migraine prevention from 1990 to 2021: a systematic literature review and meta-analysis with regression. Tepper et al. 2023

3. Doherty M, Dieppe P (2009) The "placebo" response in osteoarthritis and its implications for clinical practice. Osteoarthritis Cartilage 17(10):1255–1262. https://doi.org/10.1016/j.joca.2009.03.023

4. Vollert J, Cook NR, Kaptchuk TJ, Sehra ST, Tobias DK, Hall KT (2020) Assessment of Placebo Response in Objective and Subjective Outcome Measures in Rheumatoid Arthritis Clinical Trials. JAMA Netw Open 3(9):e2013196. https://doi.org/10.1001/jamanetworkopen.2020.13196

5. Evans K, Romero H, Spierings EL, Katz N (2021) The relation between the placebo response, observed treatment effect, and failure to meet primary endpoint: A systematic review of clinical trials of preventative pharmacological migraine treatments. Cephalalgia 41(2):247–255.

6. Sanders AE, Slade GD, Fillingim RB, Ohrbach R, Arbes SJ Jr, Tchivileva IE (2020) Effect of Treatment Expectation on Placebo Response and Analgesic Efficacy: A Secondary Aim in a Randomized Clinical Trial. JAMA Netw Open 3(4):e202907–e202907. https://doi.org/10.1001/jaman etworkopen.2020.2907

7. Zimbroff D. Patient and rater education of expectations in clinical trials (PREECT). J Clin Psychopharmacol 2001; 21: 251–252.

8. Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders Cohen et al 2021

9. Forbes RB, McCarron M, Cardwell CR (2020) Efficacy and Contextual (Placebo) Effects of CGRP Antibodies for Migraine: Systematic Review and Meta-analysis. Headache 60(8):1542–1557. https://doi.org/10.1111/ head.13907

10. Treister R, Lawal OD, Shecter JD, et al. Accurate pain reporting training diminishes the placebo response: Results from a randomised, double-blind, crossover trial. PLoS One 2018; 13: 1–12.

11. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol. 2010;52(12):1088-1097. doi:10.1111/j.1469-8749.2010.03793.xPubMedGoogle ScholarCrossref

12. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States: relation to age, income, race, and other sociodemographic factors. JAMA. 1992;267(1):64-69. doi:10.1001/jama.1992.03480010072027

13. Kroon Van Diest AM, Ernst MM, Slater S, Powers SW. Similarities and Differences Between Migraine in Children and Adults: Presentation, Disability, and Response to Treatment. Curr Pain Headache Rep. 2017 Oct 25;21(12):48. doi: 10.1007/s11916-017-0648-2. PMID: 29071512; PMCID: PMC5885754.

14. Ferro F, Gaspari C, Manfrè G, Cernigliaro F, D'Agnano D, Panzica R, Correnti E, Ruta MR, Marchese F, Pitino R, Capizzi M, Santangelo G, Versace A, Sciruicchio V, Raieli V. Children's Headache Through Drawings: A Narrative Review and a Portrait Gallery. Life (Basel). 2025 Jun 23;15(7):996. doi: 10.3390/life15070996. PMID: 40724499; PMCID: PMC12298764.

15. El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatr. 2013;167(3):250-258. doi:10.1001/jamapediatrics.2013.508Article PubMedGoogle ScholarCrossref

16. Le K, Yu D, Wang J, Ali AI, Guo Y. Is topiramate effective for migraine prevention in patients less than 18 years of age? a meta-analysis of randomized controlled trials. J Headache Pain. 2017;18(1):69. doi:10.1186/s10194-017-0776-4PubMedGoogle ScholarCrossref

17. Shamliyan TA, Kane RL, Ramakrishnan R, et al. Migraine in children: preventive pharmacologic treatments. https://www.ncbi.nlm.nih.gov/books/N

18. Powers, S.W.; Coffey, C.S.; Chamberlin, L.A.; Ecklund, D.J.; Klingner, E.A.; Yankey, J.W.; Korbee, L.L.; Porter, L.L.; Hershey, A.D. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. N. Engl. J. Med. 2017, 376, 115–124. [Google Scholar] [CrossRef] [Green Version]

19. Faria, V.; Linnman, C.; Lebel, A.; Borsook, D. Harnessing the placebo effect in pediatric migraine clinic. J. Pediatr. 2014, 165, 659–665. [Google Scholar] [CrossRef] [PubMed] [Green Version]

20. Lewis, D.W.; Winner, P.; Wasiewski, W. The placebo responder rate in children and adolescents. Headache 2005, 45, 232–239. [olume=45&pages=232%E2%80%93239&doi=10.1111/j.1526-4610.2005.05050.x"Google Scholar] [CrossRef]

21. Pablos-Mendez A, Barr RG and Shea S. Run-in periods in randomized trials: Implications for the application of results in clinical practice. JAMA 1998; 279: 222–225

22. Abu-Arafeh, I.; Hershey, A.D.; Diener, H.C.; Tassorelli, C. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine in children and adolescents, 1st edition. Cephalalgia 2019, 39, 803–816

23. Santana MJ, Manalili K, Jolley RJ, Zelinsky S, Quan H, Lu M. How to practice person-centred care: a conceptual framework. Health Expect. (2018) 21:429–40. doi: 10.1111/hex.12640

24. Olde Rikkert MGM, van der Wees PJ, Schoon Y, Westert GP. Using patient reported outcomes measures to promote integrated care. Int J Integr Care. (2018) 18:8. doi: 10.5334/ijic.3961

25. Ovretveit J, Zubkoff L, Nelson EC, Frampton S, Knudsen JL, Zimlichman E. Using patient-reported outcome measurement to improve patient care. Int J Qual Health Care. (2017) 29:874–9. doi: 10.1093/intqhc/mzx108

26. Black N. Patient reported outcome measures could help transform healthcare. BMJ. (2013) 346:f167. doi: 10.1136/bmj.f167

27. Riley AW. Evidence that school-age children can self-report on their health. Ambul Pediatr. (2004) 4(4 Suppl):371–6. doi: 10.1367/A03-178R.1

28. Haverman L, Limperg PF, Young NL, Grootenhuis MA, Klaassen RJ. Paediatric health-related quality of life: what is it and why should we measure it? Arch Dis Child. (2017) 102:393–400. doi: 10.1136/archdischild-2015-310068

29. Brunner HI, Klein-Gitelman MS, Miller MJ, Trombley M, Baldwin N, Kress A, et al. Health of children with chronic arthritis: relationship of different measures and the quality of parent proxy reporting. Arthritis Rheum. (2004) 51:763–73. doi: 10.1002/art.20689

30. Zhou H, Roberts P, Horgan L. Association between self-report pain ratings of child and parent, child and nurse and parent and nurse dyads: meta-analysis. J Adv Nurs. (2008) 63:334–42. doi: 10.1111/j.1365-2648.2008.04694.x

31. Bevans KB, Riley AW, Moon J, Forrest CB. Conceptual and methodological advances in child-reported outcomes measurement. Expert Rev Pharmacoecon Outcomes Res. (2010) 10:385–96. doi: 10.1586/erp.10.52

32. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. Value Health. (2009) 12:419–29. doi: 10.1111/j.1524-4733.2008.00470.x

33. Chambers CT, Reid GJ, Craig KD, McGrath PJ, Finley GA (1998) Agreement between child and parent reports of pain. Clin J Pain 14(4):336–342 20.

34. Vetter TR, Bridgewater CL, Ascherman LI, Madan-Swain A, McGwin GL (2014) Patient versus parental perceptions about pain and disability in children and adolescents with a variety of chronic pain conditions. Pain Res Manage 19(1):7–14

35. Tomlinson D, von Baeyer CL, Stinson JN, Sung L (2010) A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics e1168–98

36. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B (2001) The faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. Pain 93(2):173–183

37. Pozo-Rosich P, Caronna E, Sacco S, Peres MFP, Ashina S, Özge A, Ahmed F, Velez-Jimenez MK, Jenkins B, Wang SJ, Schwedt TJ, Sakai F, Levin M, Burstein R, Terwindt GM, Tassorelli C. Early treatment in migraine - A call to shift prevention from attacks to disease progression: A position statement from the International Headache Society. Cephalalgia. 2025 Oct;45(10):3331024251387721. doi: 10.1177/03331024251387721. Epub 2025 Oct 24. PMID: 41134822.

32. Sacco S, Ashina M, Diener HC, Haghdoost F, Lee MJ, Monteith TS, Jenkins B, Peres MFP, Pozo-Rosich P, Ornello R, Puledda F, Sakai F, Schwedt TJ, Terwindt G, Vaghi G, Wang SJ, Ahmed F, Tassorelli C. Setting higher standards for migraine prevention: A position statement of the International Headache Society. Cephalalgia. 2025 Feb;45(2):3331024251320608. doi: 10.1177/03331024251320608. PMID: 39980456.