

MDD Pediatric Platform Trial Background Document

This background document outlines the issues/topics to be discussed during the MDD subgroup portion of the workshop. After some general introductory points, the document covers two broad topic areas: (1) issues and challenges in pediatric MDD trial design, and (2) practical and operational challenges in setting up and conducting a pediatric MDD platform trial. Selected readings are provided for the different topics. A few readings are highlighted with a double asterisk (**) as recommended reading for all participants prior to the workshop. Other readings are provided if time and interest permits. At the end of the document, the full list of references (in alphabetical order by first author) and the abstract, when available, is provided for each reference, and all references are available on the workshop website.

Why pediatric platform trials?

The basic argument is as follows:

1. Both FDA and EMA require pediatric plans to be in place for drugs being developed for adult MDD, whether as monotherapy (both) or add-on/adjuvant (EMA; FDA with PSP waiver).

Selected References:

1. Penkov, D., P. Tomasi, I. Eichler, et al (2017). "Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States." Ther Innov Regul Sci **51**(3): 360-371.
2. Carmack, M., T. Hwang and F. T. Bourgeois (2020). "Pediatric Drug Policies Supporting Safe And Effective Use Of Therapeutics In Children: A Systematic Analysis." Health Aff (Millwood) **39**(10): 1799-1805.
2. Pediatric MDD trials are challenging. In addition, adjunctive/add-on trials, whether for MDD or a subset of MDD (i.e., insomnia, anhedonia) are especially challenging given the limited number of approved drugs for pediatric MDD, further restricting the eligible study population.



Selected References:

1. Miller, L. and J. V. Campo (2021). "Depression in Adolescents." N Engl J Med **385**(5): 445-449.
2. Fava, M. (2024). "How should we design future mechanistic and/or efficacy clinical trials?" Neuropsychopharmacology **49**(1): 197-204.
3. The current guidance about the required pediatric study designs are consistent between FDA (2018) and EMA (2023). Specifically, both agencies require a prospective randomized placebo-controlled study of 6-8 weeks duration. EMA indicates that one such trial may be adequate if the adult and pediatric efficacy data are sufficiently robust and show a similar treatment effect.

Selected References:

1. Committee for Medicinal Products for Human Use (CHMP), EMA. (2023). Guideline on clinical investigation of medicinal products in the treatment of depression.
2. Food and Drug Administration (2018). Major Depressive Disorder: Developing Drugs for Treatment - Guidance for Industry.
3. Butlen-Ducuing, F., M. Haberkamp, G. Aislaitner, et al (2023). "The new European Medicines Agency guideline on antidepressants: a guide for researchers and drug developers." Eur Psychiatry **67**(1): e2.
4. Given the common regulatory requirements and consistency in required study designs, a pediatric platform trial presents an opportunity to potentially streamline the pediatric development process and reduce the current time and operational gaps between the adult and pediatric approvals. This assumes that (a) such a trial can be designed to optimize the probability of a positive pediatric trial, and (b) the operational challenges of conducting such a study can be addressed.

Selected References:

1. **Li, Y., R. Nelson, R. Izem, et al (2024). "Unlocking the Potential: A Systematic Review of Master Protocol in Pediatrics." Ther Innov Regul Sci **58**(4): 634-644.



2. Meyer, E. L., P. Mesenbrink, C. Dunger-Baldauf, et al (2020). "The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review." *Clin Ther* **42**(7): 1330-1360.
3. Nelson, R. M., L. S. Conklin, W. J. Komocsar, et al (2022). "The Role of Master Protocols in Pediatric Drug Development." *Ther Innov Regul Sci* **56**(6): 895-902.
5. A useful distinction to guide the discussion is between a "platform trial" (i.e., study design) and a "trial -platform" (i.e., setting up the necessary operational infrastructure to conduct such a trial). Indeed, implementing a platform trial may require building a trial platform, which may lend to efficiencies in selecting sites and utilizing centralized/simultaneously utilized control groups in the context of similar and/or non-platform study designs.

How can we design a pediatric MDD platform trial to increase the probability of a positive trial?

There have been many failed pediatric clinical trials for MDD for products that have been approved for adult MDD. It is important to understand and try to correct for these failures, as building a platform trial which simply reproduced these failures would be unproductive. The general categories under which these failures can be discussed include:

1. Pediatric MDD may be fundamentally different from adult MDD so there would be no expectation that drugs which work in adult MDD would also work in pediatric MDD. In other words, are the disease, drug pharmacology and response to treatment fundamentally different between pediatric and adult MDD patients such that **extrapolation** of efficacy from adult to pediatric MDD patients is not possible? To date, neither FDA nor EMA accept the extrapolation of adult MDD safety and efficacy data to pediatric MDD patients. Does this reflect a fundamental difference in the disease, or simply the failure to date of pediatric MDD programs (except for fluoxetine (US and EU) and escitalopram (US))?

Selected References:



1. **Rice, F., L. Riglin, T. Lomax, et al (2019). "Adolescent and adult differences in major depression symptom profiles." J Affect Disord **243**: 175-181.
 2. Strawn, J. R., J. A. Mills, V. Suresh, et al (2023). "The impact of age on antidepressant response: A mega-analysis of individuals with major depressive disorder." J Psychiatr Res **159**: 266-273.
 3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2024) "Pediatric Extrapolation (E11A) - Final Version."
 4. Gamalo, M., C. Bucci-Rechtweg, R. M. Nelson, et al (2022). "Extrapolation as a Default Strategy in Pediatric Drug Development." Ther Innov Regul Sci
2. The **dosing regimens** studied in the pediatric MDD programs have not been adequately justified. Do pediatric MDD patients require unique dosing considerations to achieve the same exposure as adults with MDD? Do pediatric MDD patients require a higher exposure? In other words, the failure of the past pediatric MDD programs are a result of inadequate dosing rather than a fundamental difference in the disease between adult and pediatric MDD patients.

Selected References:

1. Findling, R. L., N. K. McNamara, R. J. Stansbrey, et al (2006). "The relevance of pharmacokinetic studies in designing efficacy trials in juvenile major depression." J Child Adolesc Psychopharmacol **16**(1-2): 131-145.
2. Hiemke, C., N. Bergemann, H. W. Clement, et al (2018). "Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017." Pharmacopsychiatry **51**(1-02): 9-62.
3. Namerow, L. B., L. B. Ramsey, S. Malik, et al (2022). "Editorial: Beyond Red Light, Green Light: Examining the Role of Pharmacogenomics in Evidence-Based Care in Child and Adolescent Psychiatry." J Am Acad Child Adolesc Psychiatry **61**(1): 29-31.
4. Shibata, R. Y., R. Kubota, K. Uenaka, et al (2023). "Population pharmacokinetics of duloxetine in Japanese pediatric patients with major depressive disorder." Drug Metab Pharmacokinet **51**: 100496.



5. Strawn, J. R., E. A. Poweleit, C. R. S. Uppugunduri and L. B. Ramsey (2021). "Pediatric Therapeutic Drug Monitoring for Selective Serotonin Reuptake Inhibitors." *Front Pharmacol* **12**: 749692.
6. Tini, E., L. Smigielski, M. Romanos, et al (2022). "Therapeutic drug monitoring of sertraline in children and adolescents: A naturalistic study with insights into the clinical response and treatment of obsessive-compulsive disorder." *Compr Psychiatry* **115**: 152301.
3. Are the failed pediatric trials due to a higher **placebo response** such that the trials were inadequate to detect a separation between the active treatment and placebo? Would this be addressed by a larger sample size, or by a design that enriched for placebo non-responders? Would a run-in period of placebo and psychological therapy reduce the placebo rate? How have placebo lead-ins worked in psychiatry and child psychiatry trials in the past? What would be the impact on the generalizability of the study results? How does the design of the placebo phase impact on blinding?

Selected References:

1. Feeney, A., R. S. Hock, M. Fava, et al (2022). "Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis." *J Affect Disord* **305**: 55-64.
2. Li, Y., J. Huang, Y. He, J. Yang, et al (2019). "The Impact of Placebo Response Rates on Clinical Trial Outcome: A Systematic Review and Meta-Analysis of Antidepressants in Children and Adolescents with Major Depressive Disorder." *J Child Adolesc Psychopharmacol* **29**(9): 712-720.
3. Meister, R., M. Abbas, J. Antel, et al (2020). "Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis." *Eur Child Adolesc Psychiatry* **29**(3): 253-273.
4. Mossman, S. A., J. A. Mills, et al (2021). "The Impact of Failed Antidepressant Trials on Outcomes in Children and Adolescents with Anxiety and Depression: A Systematic Review and Meta-Analysis." *J Child Adolesc Psychopharmacol* **31**(4): 259-267.



5. Okubo, R., K. Matsui and M. Narukawa (2023). "Factors Related to Placebo Response in Randomized, Double-Blind Clinical Trials of Antidepressants in Children and Adolescents: A Meta-regression Analysis." Clin Drug Investig **43**(6): 383-391.
 6. Radecki, D. T., W. Z. Robieson, M. Gopalkrishnan, et al (2024). "Safety and Efficacy of Levomilnacipran Extended Release in Pediatric Patients Aged 7-17 Years with Major Depressive Disorder: Results of Two Phase 3, Randomized, Double-Blind Studies." J Child Adolesc Psychopharmacol **34**(5): 241-250.
 7. Scott, A. J., L. Sharpe, V. Quinn and B. Colagiuri (2022). "Association of Single-blind Placebo Run-in Periods With the Placebo Response in Randomized Clinical Trials of Antidepressants: A Systematic Review and Meta-analysis." JAMA Psychiatry **79**(1): 42-49.
 8. Walkup, J. T. (2017). "Antidepressant Efficacy for Depression in Children and Adolescents: Industry- and NIMH-Funded Studies." Am J Psychiatry **174**(5): 430-437.
4. Are there **biomarkers and/or predictors of response** which would define a population which would potentially be more responsive to treatment? Could these be used as "bridging biomarkers" to support extrapolation from adult to pediatric MDD patients? Currently, there are no biomarkers which have been established for these purposes. However, can a pediatric MDD platform trial be designed to include the development of biomarkers as an exploratory objective to advance the field in the future? Are there better criteria of predictors of response which could be used to increase the probability of success?

Selected References:

1. Kim, K. M., K. H. Lee, H. Kim, et al (2024). "Symptom clusters in adolescent depression and differential responses of clusters to pharmacologic treatment." J Psychiatr Res **172**: 59-65.
2. Jones, C. and C. B. Nemeroff (2021). "Precision Psychiatry: Biomarker-Guided Tailored Therapy for Effective Treatment and Prevention in Major Depression." Adv Exp Med Biol **1305**: 535-563.
3. Lee, J., S. Chi and M. S. Lee (2021). "Molecular Biomarkers for Pediatric Depressive Disorders: A Narrative Review." Int J Mol Sci **22**(18).



4. Perna, G., A. Spiti, T. Torti, et al (2024). "Biomarker-Guided Tailored Therapy in Major Depression." Adv Exp Med Biol **1456**: 379-400.
 5. Suseelan, S. and G. Pinna (2023). "Heterogeneity in major depressive disorder: The need for biomarker-based personalized treatments." Adv Clin Chem **112**: 1-67.
 6. Stone, M. B., Z. S. Yaseen, B. J. Miller, et al (2022). "Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis." Bmj **378**: e067606.
 7. Winter, N. R., J. Blanke, R. Leenings, et al (2024). "A Systematic Evaluation of Machine Learning-Based Biomarkers for Major Depressive Disorder." JAMA Psychiatry **81**(4): 386-395.
 8. Wu, W., Y. Zhang, J. Jiang, et al (2020). "An electroencephalographic signature predicts antidepressant response in major depression." Nat Biotechnol **38**(4): 439-447.
 9. Yang, Z., C. Gao, Z. Li, et al (2024). "The changes of tPA/PAI-1 system are associated with the ratio of BDNF/proBDNF in major depressive disorder and SSRIs antidepressant treatment." Neuroscience.
 10. Zwolińska, W., M. Dmistrz-Węglarz and A. Słopeń (2023). "Biomarkers in Child and Adolescent Depression." Child Psychiatry Hum Dev **54**(1): 266-281.
5. Would platform trials be limited to either monotherapy and/or "add on" treatments? Is there a platform design which could include different subpopulation(s) based on the predominant manifestation of MDD, e.g., insomnia or anhedonia? How does one design an adjunctive trial given the limited number of approved medications for children and adolescents with MDD? What is the role of psychotherapy in a pediatric MDD platform trial - background or treatment arm?

Selected References:

1. Psychotherapy: Cuijpers, P., E. Karyotaki, M. Ciharova, et al (2023). "The effects of psychological treatments of depression in children and adolescents on response, reliable change, and deterioration: a systematic review and meta-analysis." Eur Child Adolesc Psychiatry **32**(1): 177-192.



2. Gupta, T., K. L. Eckstrand and E. E. Forbes (2024). "Annual Research Review: Puberty and the development of anhedonia - considering childhood adversity and inflammation." J Child Psychol Psychiatry **65**(4): 459-480.
3. Drevets, W. C., G. M. Wittenberg, E. T. Bullmore and H. K. Manji (2022). "Immune targets for therapeutic development in depression: towards precision medicine." Nat Rev Drug Discov **21**(3): 224-244.
6. There are some well-known challenges which must be addressed in the design of any platform trial, but these are not specific to MDD. For example, regulatory agencies may only accept using concurrent placebo controls in the analysis of the treatment effect of an investigational drug. This may limit the inferential advantages of a platform trial depending on the number of drugs which are being studied concurrently. Given the limited time in the workshop, the intent is not to discuss these more general challenges unless there is a specific implication for addressing these challenges in the context of pediatric MDD.

What are the operational challenges to setting up a pediatric MDD platform trial, and how can they be addressed?

1. The establishment of clinical trial networks tries to address the historical approach of setting up trial networks on a study-by-study basis, which is highly inefficient. These "platform trial networks" also could serve as a trial network for non-platform studies. EU-PEARL developed the concept of an "integrated research platform" to support the development and execution of platform trials. There are also pediatric-specific clinical trial networks which are being developed (e.g., c4c in Europe and I-ACT4C in the US). To what extent can a pediatric MDD platform trial use these existing pediatric networks, or does an MDD-specific network need to be developed?

Selected References:

1. **Nguyen, Q. L., K. Hees, S. Hernandez Penna, et al (2024). "Regulatory Issues of Platform Trials: Learnings from EU-PEARL." Clin Pharmacol Ther **116**(1): 52-63.



2. Koenig, F., C. Spiertz, D. Millar, et al (2024). "Current state-of-the-art and gaps in platform trials: 10 things you should know, insights from EU-PEARL." *EClinicalMedicine* **67**: 102384.
 3. Dhaenens, B. A. E., F. Mahler, H. Batchelor, et al (2023). "Optimizing expert and patient input in pediatric trial design: Lessons learned and recommendations from a collaboration between conect4children and European Patient-Centric Clinical Trial Platforms." *Clin Transl Sci* **16**(8): 1458-1468.
2. Separate from the question of the clinical trial infrastructure is the "sponsor" of the platform trial. A platform trial is structured as a "master protocol" with multiple intervention-specific appendices (ISAs). In general, FDA prefers that the master protocol and ISAs be submitted to one IND to simplify review and streamline communication. However, this requires that the "owner" of each investigational drug give up "control" of the program to a third party as the IND sponsor. For this reason, third-party platform trials have generally focused on phase 2 (proof-of-concept) and phase 4 (e.g., post-marketing comparative effectiveness) studies, rather than phase 3 registrational trials. Although the pediatric trials required under a PIP and/or PSP could be considered registrational (as they are intended to obtain pediatric approval/labeling), would industry sponsors be reluctant to include these products in an appropriately designed platform trial? Would the regulatory requirements established under a PIP and/or PSP provide a sufficient structure so that ceding "control" to a third-party would be less of a concern?

Selected Reference:

1. Food and Drug Administration (2023). Master Protocols for Drug and Biological Product Development - Guidance for Industry. US Department of Health and Human Services.
3. The involvement of a Contract Research Organization (CRO) increases the costs of a clinical trial (by up to 30% by some estimates) when compared to an internally run clinical trial. In addition, the fee-for-service model may serve as a disincentive for efficient performance. Presumably some of these increased costs would be reduced and/or eliminated if there is an established clinical trial network for the pediatric MDD platform. A trial network may additionally provide some quality control, and a mechanism to efficiently recruit sites and improve recruitment more generally. These issues are not unique to pediatric MDD. Are there issues which should be considered in the context of pediatric MDD which would either exacerbate or mitigate these concerns?



Selected References:

1. Pergolizzi, J., Jr., C. Pergolizzi and J. A. K. LeQuang (2023). "Pirates of Clinical Trials." Cureus 15(10): e47819.
2. Wasan, H., D. Singh, K. H. Reeta, P. Gupta and Y. K. Gupta (2022). "Drug development process and COVID-19 pandemic: Flourishing era of outsourcing." Indian J Pharmacol 54(5): 364-372.

FINAL DRAFT

