Best Pharmaceuticals for Children Act (BPCA) Framework to Enable Pediatric Drug Development

Resources Lists

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NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Best Pharmaceuticals for Children Act (BPCA)

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Introduction

The National Institutes of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) Program (https://www.nichd.nih.gov/research/supported/bpca/history) has, for the last 18 years, sponsored a pediatric drug development program of off patent medications used in children. The primary goals of the program include identifying existing needs in pediatric therapeutics, prioritizing those needs, sponsoring clinical studies to improve dosing, safety and effectiveness data in those prioritized areas, and submitting the clinical study data to the FDA for potential drug label updates that aim to improve the knowledge of medications used in children. The Program has been very successful in its mandate to improve knowledge gaps and has, to date, conducted over 40 clinical trials which include more than 200 molecules, provided data to the FDA in the form of clinical study reports for over 26 molecules, and achieved 17 label changes.

In early 2020, the Program conducted an analysis of the metrics and outcomes of the clinical program, including prioritization goals, study outcomes, and remaining gaps in pediatric therapeutics. As part of that analysis, the Program reviewed historical data from past prioritizations and previous BPCA working groups to determine remaining and unaddressed therapeutic gaps in knowledge (2008-2018). Many topics of interests and unanswered questions arose from this review, but one recurring theme stood out as a potential actionable item:

Is it possible to develop **a generic framework** that:

- **can be useful to and utilized by various stakeholder involved in pediatric drug development/research, and that**
- **can subsequently be customized to specific therapeutic areas, indications, type of drug, developmental stages, and phenotypic expression?**

As a part of the initiation of this call for a generic framework of resources, the NIH BPCA Program held its annual Stakeholders Meeting on December 14-15, 2020 and discussed this concept with our stakeholders. At that meeting, the NIH staff and the Pediatric Trials Network (https://pediatrictrials.org/) investigators provided updates on the current progress within the clinical program and then held breakout sessions focused on drug development issues identified as part of the BPCA analysis as remaining scientific gaps in pediatric drug development. Meeting minutes can be found here: https://www.nichd.nih.gov/sites/default/files/inline-files/BPCA12-15-2020StakeholdMeetSum.pdf.

Since the meeting in December 2020, development of the BPCA Framework to Enable Pediatric Drug Development, spearheaded by the NICHD BPCA Program, has made steady progress throughout 2021. Subject matter experts in pediatric care collaborated to research, identify, submit and review available resources of scientific articles, book chapters, and reports. The framework will give stakeholders involved in pediatric therapeutics research, including new and junior investigators applying for grants, access to a multitude of resources to review prior to writing grant proposals and/or before conducting pediatric drug development research. The goal is to have an annotated, selected, and curated collection of resources that will indicate which resources are essential, "read this first," and when other resources will be useful. Resources of universal interest will be identified along with resources that relate to specific topics in pediatric drug development and to specific clinical populations.

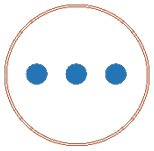
Resource Focus Areas

- General Pediatric Drug Development Resources and Guidances
- Advancing Clinical Trial Designs and Conduct in Pediatric Drug Development
- Emphasizing Pharmacodynamic Biomarkers in Pediatric Drug Development
- Enhancing Research in Pediatric-Friendly Formulations
- The Relevance of Pharmacoepidemiology in Informing Pediatric Drug Development
- How Pharmacokinetic Modeling Can Be Used to Inform Drug Dosing
- The Role of Quantitative Systems Pharmacology in Pediatric Drug Development

Resource Classifications

Read This First
Essential overview documents

Helpful Explanation
Resources that offer further explanation



Additional Resources
Resources for specific situations or are not public

U.S. Guidances
Relevant FDA guidance documents

Stakeholder Impact

Pediatric drug development encompasses a vast variety of stakeholders engaged in expanding research knowledge, as well as improving outcomes, access and public health impact. These various stakeholders could certainly benefit from increased efficiency of access to documents as well as the possibility of and increased likelihood of useful contributions to each other's work. The table below describes benefits to stakeholders involved with the framework.

Stakeholders	Benefits
Clinical Investigators	Greater understanding of the impact of drug labelling and increasing knowledge of study design and conduct choices
Preclinical Investigators	Identifying potential mechanisms for targeted contributions to clinical work so that can be applied optimally
Regulators	Greater awareness of the expanse of resources available to and utilized by researchers
Patients and their advocates	Increased awareness of the science behind clinical research and the importance of improving drug labeling
Organizations (industry and others) **that own assets for pediatric drug development** (drugs, biomarkers, pre-clinical models, etc.)	Improved clarity about pathways to regulatory approval and more informed contributions from investigators
Institutions (industry and others) **that drive drug development** (Sponsors) and **Institutions** (industry and others) **that support drug development** (e.g., Contract Research Organizations or Academic Research Organizations)	More informed contributions from investigators as a result of access to relevant guidance

Program Leaders

Perdita Taylor-Zapata, M.D., is a Physician with the Obstetric and Pediatric Pharmacology and Therapeutics Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), where she leads the effort for the implementation of the Best Pharmaceuticals for Children Act (BPCA) at the NICHD. She is a pediatrician from the Washington Metropolitan area. She graduated from Howard University Medical School in 1994, and completed her pediatric residency training at the Children's National Medical Center in Washington, D.C. After her residency, she worked at the National Institutes of Health Clinical Center as a clinic physician in the Pediatric HIV Working Group of the National Cancer Institute. There she spent 7 years taking care of the outpatient and inpatient medical needs of the HIV-positive pediatric patients enrolled in phase I/II clinical treatment trials. In addition to her role as a staff physician, she was also involved in medical research, writing parts of clinical protocols and conducting retrospective and prospective research projects. Since 2004, she has worked in OPPTB, starting as the primary outreach liaison for the BPCA Program, then as the Program official for the BPCA Data Coordinating Center (DCC), and now as the primary program lead for the entire BPCA Program, including the Pediatric Trials Network, the DCC and the logistics contract team. In addition to pediatric drug development, Dr. Taylor-Zapata also has research interests in pharmacoepidemiology, workforce diversity, and adverse effects of medications used in children.

Mark Turner, Ph.D., MBChB, is Professor of Neonatology and Research Delivery at the University of Liverpool, UK. He graduated from Manchester University with a medical degree in 1991 and a PhD in 1999 (placental physiology). He trained in neonatal medicine in the North West of England and has worked as a Consultant Neonatologist in Liverpool since 2005. His research aims to improve the access of newborn babies and children to high quality medicines. This has included studies of dosing, safety and efficacy, and research about excipients, manipulations of medicines, the avoidability of adverse drug reactions and the value of age-appropriate formulations. He believes that the coherent integration of the design and conduct of clinical trials is key to improving the quality of medicines. He works to develop efficient medicines research infrastructure in Europe and globally as Chair of the European Network for Paediatric Research at the European Medicines Agency (EnprEMA) (2013 – 2019), Convenor of the European Paediatric Clinical Trials Research Infrastructure, co-Director of the International Neonatal Consortium and as co-Coordinator of the Collaborative Network for European Clinical Trials for Children (conect4children, c4c).

General Resources in Pediatric Drug Development (PDD)

Read this First

1) E8(R1) General Considerations for Clinical Studies
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies

2) Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population
FDA. 2000.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population

3) General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
FDA. 2014.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products

4) Clinical Trials in Children
Joseph PD, Craig JC, Caldwell PH. *Br J Clin Pharmacol*. 2015.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4345947/

Helpful Explanation

1) Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND
FDA. 2013.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be

2) Toolkit for Research and Development of Paediatric Antiretroviral Drugs and Formulations
World Health Organization. 2018.
https://www.who.int/publications/i/item/9789241514361

3) Reflection Paper on the Use of Extrapolation in the Development of Medicines for Pediatrics
EMA. 2018.
https://www.ema.europa.eu/en/extrapolation-efficacy-safety-paediatric-medicine-development#current-version-section

4) Frameworks for Evaluating Medicines in Children
Turner MA, Hirschfeld S. *Clin Ther*. 2017.
https://www.clinicaltherapeutics.com/article/S0149-2918(17)30946-3/fulltext

5) Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation.
EFPIA MID3 Workgroup. *CPT Pharmacometrics Syst Pharmacol.* 2016.
https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12049

6) Rare Pediatric Disease Priority Review Vouchers
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-pediatric-disease-priority-review-vouchers

7) Safety, Dosing, and Pharmaceutical Quality for Studies That Evaluate Medicinal Products (Including Biological Products) in Neonates.
Ward RM, Benjamin D, Barrett JS, Allegaert K, Portman R, et al. *Pediatr Res.* 2017.
https://www.nature.com/articles/pr2016221

8) Pediatric Drug Development Regulatory Considerations
FDA. 2016.
https://www.fda.gov/media/100571/download

9) Office of New Drugs Regulatory Science Research Homepage
FDA. 2022
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs-regulatory-science-research

U.S. Guidances

1) Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

2) E11A Pediatric Extrapolation
FDA. 2022
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation

3) Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
FDA. 2020.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

4) Exception from Informed Consent Requirements for Emergency Research
FDA. 2013.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research

5) Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices
FDA. 2016.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-existing-clinical-data-extrapolation-pediatric-uses-medical-devices

6) COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders
FDA. Last accessed January 20, 2022.
https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

7) Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans
FDA. 2020.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

8) General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance

Additional Resources

1) Preclinical Efficacy in Therapeutic Area Guidelines from the U.S. Food and Drug Administration and the European Medicines Agency: A Cross-Sectional Study.
Langhof H, Chin WWL, Wieschowski S, Federico C, Kimmelman J, et al. *Br J Pharmacol*. 2018.
https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.14485

2) Informed Consent
FDA. 2014.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

3) Exploratory IND Studies
FDA. 2006.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exploratory-ind-studies

4) Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff
FDA. 2018.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biomarker-qualification-evidentiary-framework

5) How to Comply with the Pediatric Research Equity Act
FDA. 2005.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-comply-pediatric-research-equity-act

6) Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good

7) Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States.
Penkov D, Tomasi P, Eichler I, Murphy D, Yao LP, Temeck J. *Ther Innov Regul Sci.* 2017.
https://pubmed.ncbi.nlm.nih.gov/28674673/

Advancing Clinical Trial Designs and Conduct in PDD

Read this First

1) Inclusion of Adolescents in Adult Clinical Trials: Report of the Institute for Advanced Clinical Trials for Children's Pediatric Innovation Research Forum.
Noel GJ, Nelson RM, Bucci-Rechtweg C, Portman R, Miller T, et al. *Ther Innov Regul Sci.* 2021.
https://doi.org/10.1007/s43441-021-00283-y

2) How to Conduct Clinical Trials in Children: A Tutorial.
Shakhnovich V, Hornik CP, Kearns GL, Weigel J, Abdel-Rahman SM. *Clin Transl Sci.* 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6510379/

3) CTTI PROJECT: Master Protocol Studies
Clinical Trials Transformation Initiative. Last accessed January 20, 2022.
https://www.ctti-clinicaltrials.org/projects/master-protocol-studies

4) Small Clinical Trials: Issues and Challenges.
Evans CH Jr., Ildstad ST, editors. *National Academies Press (US)*. 2001.
https://www.ncbi.nlm.nih.gov/books/NBK223331/

5) Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls.
Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. *Clin Pharmacol Ther.* 2007.
https://pubmed.ncbi.nlm.nih.gov/17329988/

Helpful Explanation

1) A Roadmap to Using Historical Controls in Clinical Trials—by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG)
Ghadessi M, Tang R, Zhou J, Liu R, Wang C, et al. *Orphanet Journal of Rare Diseases*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7069184/

2) Innovative Study Designs Optimizing Clinical Pharmacology Research in Infants and Children
Balevic SJ, Cohen-Wolkowiez M. *J Clin Pharmacol.* 2018.
https://accp1.onlinelibrary.wiley.com/doi/epdf/10.1002/jcph.1053

3) Multiple Endpoints in Clinical Trials Guidance for Industry
FDA. 2022
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry

4) Systematic Review of Basket Trials, Umbrella Trials, and Platform Trials: A Landscape Analysis of Master Protocols.
Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, et al. *Trials*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6751792/

5) Moving Forward in Clinical Research with Master Protocols
Park JJH, Dron L, Mills EJ. *Contemp Clin Trials.* 2021.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8120789/

6) Informational Designs and Potential Applications to Rare Disease. In "Handbook of Biomarkers and Precision Medicine"
Beckman, RA, Chen C. *Chapman and Hall/CRC*. 2019. pp 183-188.
https://u1lib.org/book/5410008/67f76d

7) FDA's Clinical Investigator Course Preparing an IND Application: CBER Breakout Session; Putting Together Your IND Submission (CBER): Preclinical Considerations; Clinical Trial Design Expectations to Ensure Safety for a First-in-Human Clinical Investigation
FDA. 2019.
https://cersi.umd.edu/sites/cersi.umd.edu/files/D3S06-Fink-Galvio-Belsky-v1.pdf

8) Plan and Design with the Child in Mind: Global Pediatric Clinical Trials Network Recommendations and Insights for Sponsors of Pediatric Research
Duke Clinical Research Institute. 2019.
https://dcri.org/wp-content/uploads/2019/11/GPTN-whitepaper_07nov2019.pdf

9) Best Practices for Adaptive Trials
Global Clinical Supplies Group. 2019.
https://mygcsg.com/wp-content/uploads/2019/04/GCSG-2019_Workshop-8_Best-Practices-for-Adaptive-Trials.pdf

10) European Regulators' View on Platform Trials
Paul-Ehrlich-Institut. 2018.
https://www.efspi.org/Documents/Events/Events%202018/3rd_RegStat/32%20Hofner.pdf

Helpful Explanation - Specific Situations

Oncology

1) Clinical Pharmacology in the Adolescent Oncology Patient.
Veal GJ, Hartford CM, Stewart CF. *J Clin Oncol*. 2010.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018345/

2) Joint Adolescent-Adult Early Phase Clinical Trials to Improve Access to New Drugs for Adolescents with Cancer: Proposals from the Multi-Stakeholder Platform-ACCELERATE.
Gaspar N, Marshall LV, Binner D, Herold R, Rousseau R, et al., Members of Working Group 1 of the Paediatric Platform of ACCELERATE. *Ann Oncol.* 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889024/

3) Dose Titration Algorithm Tuning (DTAT) Should Supersede 'the' Maximum Tolerated Dose (MTD) in Oncology Dose-Finding Trials
Norris DC. *F1000Research.* 2017.
https://f1000research.com/articles/6-112/v3

4) ACCELERATE Platform Links - Fostering Age Inclusive Research (FAIR) Trials
ACCELERATE. Last accessed January 20, 2022.
https://www.accelerate-platform.org/fair-trials/

5) Trial Designs for Rare Diseases and Small Sample Sizes in Oncology. In "Textbook of Clinical Trials in Oncology: A Statistical Perspective." Beckman RA, Chen C, Posch M, Zohar S. *Chapman & Hall/CRC Press*. 2019. pp. 297-316.
https://dokumen.pub/textbook-of-clinical-trials-in-oncology-a-statistical-perspective-9781138083776-1138083771-9781315112084.html

Cell and Gene Therapy

1) Expediting Clinical Development for Cell and Gene Therapies - Applying Master Protocol Concept in Early-Phase Trials
Liu K. *Sana Biotechnology*. 2021.
https://www.med.upenn.edu/cellicon2021/assets/user-content/documents/ke-liu-cellicon-valley-conference-may-6-2021-(1).pdf

2) Issues in Clinical Trial Design for Cell Therapy
FDA. 2019.
https://pharm.ucsf.edu/sites/pharm.ucsf.edu/files/acdrs/media-browser/Issues%20in%20Clinical%20Trial%20Design%20for%20Cell%20Therapies.pdf

3) Adaptive Dose-Finding Based on Safety and Feasibility in Early-Phase Clinical Trials of Adoptive Cell Immunotherapy
Wages NA, Fadul CE. *Clin Trials.* 2020
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211137/

4) Exploring Novel Clinical Trial Designs for Gene-Based Therapies: Proceedings of a Workshop.
Beachy SH, Alper J, Hackmann M, Addie S, editors. *National Academies Press*. 2020.
https://pubmed.ncbi.nlm.nih.gov/32730016/

Infections

1) Towards Early Inclusion of Children in Tuberculosis Drugs Trials: A Consensus Statement.
Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, et al. *Lancet Infect Dis*. 2015.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471052/

2) Meeting the Goal of Concurrent Adolescent and Adult Licensure of HIV Prevention and Treatment Strategies
Hume M, Lewis LL, Nelson RM. *J Med Ethics.* 2017.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5685924/

3) The HIV Drug Optimization Agenda: Promoting Standards for Earlier Investigation and Approvals of Antiretroviral Drugs for Use in Adolescents Living with HIV
Rojo P, Carpenter D, Venter F, Turkova A, Penazzato M. *J Int AIDS Soc*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7459170/

4) Model Informed Drug Development Approaches for Immunogenicity Assessments Workshop
FDA. 2021.
https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/model-informed-drug-development-approaches-immunogenicity-assessments-06092021-06092021

Neonates

1) Clinical Trials of Medicines in Neonates: The Influence of Ethical and Practical Issues on Design and Conduct
Turner MA. *Br J Clin Pharmacol.* 2015.
https://pubmed.ncbi.nlm.nih.gov/25041601/

Additional Resources

1) Platform Trials in Drug Development: Umbrella Trials and Basket Trials.
Antonijevic Z, Beckman RA, editors, *Chapman & Hall/CRC*. 2018.
https://www.routledge.com/Platform-Trial-Designs-in-Drug-Development-Umbrella-Trials-and-Basket-Trials/Antonijevic-Beckman/p/book/9780367732639

2) Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs
Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, et al. *Pediatrics*. 2011.
https://pubmed.ncbi.nlm.nih.gov/22025597/

3) Rare Diseases: Common Issues in Drug Development Guidance for Industry
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry

4) Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products

5) Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices
FDA. 2016.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-existing-clinical-data-extrapolation-pediatric-uses-medical-devices

6) E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population
FDA. 2018.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population

7) Clinical Trials Guidance Documents
FDA. Last accessed January 20, 2022.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents

8) E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials: Guidance for Industry
FDA. 2021.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

9) Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
FDA. 2020.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial

10) S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals
FDA. 2021.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s11-nonclinical-safety-testing-support-development-pediatric-pharmaceuticals

11) Incorporating Adult Evidence into Pediatric Research and Practice: Bayesian Designs to Expedite Obtaining Child-Specific Evidence.
Murthy S, Fontela P, Berry S. *JAMA*. 2021.
https://pubmed.ncbi.nlm.nih.gov/33900369/

12) Integrating Predictive Biomarkers and Classifiers into Oncology Clinical Development Programmes.
Beckman RA, Clark J, Chen C. *Nature Reviews Drug Discovery*. 2011.
https://pubmed.ncbi.nlm.nih.gov/21959287/

13) Adaptive Design for a Confirmatory Basket Trial in Multiple Tumor Types Based on a Putative Predictive Biomarker.
Beckman RA, Antonijevic Z, Kalamegham R, Cong C. *Clin Pharmacol Ther*. 2016.
https://pubmed.ncbi.nlm.nih.gov/27509351/

14) Statistical Design and Considerations of a Phase 3 Basket Trial for Simultaneous Investigation of Multiple Tumor Types in One Study.
Chen C, Li N, Yuan S, Antonijevic Z, Kalamegham R, et al. *Statistics in Biopharmaceutical Research*. 2016.
https://www.tandfonline.com/doi/full/10.1080/19466315.2016.1193044?scroll=top&needAccess=true

Emphasizing Developmental Pharmacodynamics Biomarkers in PDD

Read this First

1) Biomarkers and Surrogate Endpoints.
Aronson JK. *Br J Clin Pharmacol*. 2005.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884846/

2) Useful Pharmacodynamic Endpoints in Children: Selection, Measurement, and Next Steps
Kelly LE, Sinha Y, Barker CIS, Standing JF, Offringa M. *Pediatr Res*. 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023695/

3) Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure
FDA. 2021.
https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

4) BEST (Biomarkers, EndpointS, and other Tools) Resource.
FDA. Updated 2021.
https://www.ncbi.nlm.nih.gov/books/NBK338449/

5) Surrogate Endpoints in Pediatric Studies Submitted to the US FDA.
Green DJ, Sun H, Burnham J, Liu XI, van den Anker J, et al. *Clin Pharmacol Ther*. 2019.
https://pubmed.ncbi.nlm.nih.gov/30094815/

6) Pediatric Clinical Endpoint and Pharmacodynamic Biomarkers: Limitations and Opportunities. Dinh JC, Hosey-Cojocari CM, Jones BL. *Paediatr Drugs*. 2020. https://rdcu.be/cA6Y4

Helpful Explanation

1) Pharmaco fMRI: Determining the Functional Anatomy of The Effects of Medication. Wandschneider B, Koepp MJ. *Neuroimage Clin*. 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5067101/

2) Designing Clinical Trials in Pediatric Nonalcoholic Steatohepatitis: Tips for Patient Selection and Appropriate Endpoints. Alkhouri N, Kohli R, Feldstein AE. *Hepatol Commun*. 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6887671/

3) FDA Biomarker Qualification Guidance *FDA*. 2021. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program

4) FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry *FDA*. 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fdara-implementation-guidance-pediatric-studies-molecularly-targeted-oncology-drugs-amendments-sec

5) Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims *FDA*. 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

6) Biomarkers and Surrogate Endpoints in Drug Development: A European Regulatory View Wickstrom K, Moseley J. *Invest Ophthalmol Vis Sci.* 2017. https://iovs.arvojournals.org/article.aspx?articleid=2625915

7) The Emerging Role of Cell-Free DNA as a Molecular Marker for Cancer Management Bronkhorst AJ, Ungerer V, Holdenrieder S. *Biomol Detect Quantif*. 2019. https://pubmed.ncbi.nlm.nih.gov/30923679/

8) Challenges of Diagnosing Antibody-Mediated Rejection: The Role of Invasive and Non-Invasive Biomarkers Krishnamoorthy S, Kyeso Y. *Medicina (Kaunas)*. 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8147623/

Enhancing Research in Pediatric-Friendly Formulations

Read this First

1) Playing Hide and Seek with Poorly Tasting Paediatric Medicines: Do Not Forget the Excipients.
Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, et al. *Adv Drug Deliv Rev*. 2014.
https://www.sciencedirect.com/science/article/pii/S0169409X14000349?via%3Dihub

2) Making Medicines Baby Size: The Challenges in Bridging the Formulation Gap in Neonatal Medicine
O'Brien F, Clapham D, Krysiak K, Batchelor H, Field P, et al. *Int J Mol Sci*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600135/

3) Drug Formulations: Standards and Novel Strategies for Drug Administration in Pediatrics
Thabet Y, Klingmann V, Breitkreutz J. *J Clin Pharmacol*. 2018.
https://accp1.onlinelibrary.wiley.com/doi/full/10.1002/jcph.1138

4) Development of Paediatric Medicines: Points to Consider in Formulation
World Health Organization. 2012.
https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex5TRS-970.pdf?ua=1

Helpful Explanation

1) Advances in Drug Delivery Systems: Work in Progress Still Needed?
Laffleur F, Keckeis V. *Int J Pharm X*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305387/

2) Formulation Approaches to Pediatric Oral Drug Delivery: Benefits and Limitations of Current Platforms
Lopez FL, Ernest TB, Tuleu C, Gul MO. *Expert Opin Drug Deliv*. 2015.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4673516/

3) Co-administration of Paediatric Medicines with Food and Drinks in the Context of Their Physicochemical Properties - A Global Perspective on Practices and Recommendations.
Martir J, Flanagan T, Mann J, Fotaki N. *AAPS J*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7056676/

4) Patient Centric Pharmaceutical Drug Product Design-The Impact on Medication Adherence.
Menditto E, Orlando V, De Rosa G, Minghetti P, Musazzi UMet al. *Pharmaceutics*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7023035/

5) Sweetener Content and Cariogenic Potential of Pediatric Oral Medications: A Literature.
Al Humaid J. *Int J Health Sci (Qassim)*. 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969777/

6) Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products: Safety Qualification of Excipients
Buckley LA, Salunke S, Thompson K, Baer G, Fegley D, et al. *Int J Pharm*. 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771984/

7) Toolkit For Research and Development of Paediatric Antiretroviral Drugs and Formulations
WHO and UNITAID in Collaboration with IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network, PENTA (Paediatric European Network for Treatment of AIDS) foundation and experts from the Paediatric Antiretroviral Working Group.
World Health Organization. 2018.
http://apps.who.int/iris/bitstream/handle/10665/273151/9789241514361-eng.pdf?ua=1

8) Innovations in Pediatric Drug Formulations and Administration Technologies for Low Resource Settings
Gerrard SE, Walsh J, Bowers N, Salunke S, Hershenson S. *Pharmaceutics*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6835316/

Additional Resources

1) Acceptability of Uncoated Mini-Tablets in Neonates--A Randomized Controlled Trial
Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, et al. *J Pediatr.* 2015.
https://pubmed.ncbi.nlm.nih.gov/26259675/

2) Best Practice Recommendations Regarding the Assessment of Palatability and Swallowability in the Development of Oral Dosage Forms for Pediatric Patients
Thompson C, Lombardi D, Sjostedt P, Squires L. *Ther Innov Regul Sci.* 2015.
https://pubmed.ncbi.nlm.nih.gov/30227032/

3) Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations

4) Bioavailability Studies Submitted in NDAs or INDs – General Considerations
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations

5) Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
FDA. 2018.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-liquids-andor-soft-foods-vehicles-drug-administration-general-considerations-selection-and-vitro

6) Pharmaceutical Development of Medicines for Paediatric Use
European Medicines Agency. 2013.
https://www.ema.europa.eu/en/pharmaceutical-development-medicines-paediatric-use

7) Harnessing Formulation and Clinical Pharmacology Knowledge for Efficient Pediatric Drug Development: Overview and Discussions from M-CERSI Pediatric Formulation Workshop 2019
Khong YM, Liu J, Cook J, Purohit V, Thompson K, et al. *Eur J Pharm Biopharm.* 2021.
https://pubmed.ncbi.nlm.nih.gov/33878434/

8) Pediatric Formulation Development - Challenges of Today and Strategies for Tomorrow: Summary Report from M-CERSI Workshop 2019
Tan DCT, Khong YM, Mount S, Galella E, Mitra B, et al. *Eur J Pharm Biopharm*. 2021
https://pubmed.ncbi.nlm.nih.gov/33878432/

The Relevance of Pharmacoepidemiology Studies in Informing PDD

Read this First

1) Real-World Evidence to Assess Medication Safety or Effectiveness in Children: Systematic Review
Lasky T, Carleton B, Horton DB, Kelly LE, Bennett D, et al. *Drugs Real World Outcomes.* 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7221095/

2) Big Data in the Assessment of Pediatric Medication Safety
McMahon AW, Cooper WO, Brown JS, Carleton B, Doshi-Velez F, et al. *Pediatrics*. 2020.
https://pediatrics.aappublications.org/content/145/2/e20190562.long

3) Specifying a Target Trial Prevents Immortal Time Bias and Other Self-Inflicted Injuries in Observational Analyses
Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. *J Clin Epidemiol.* 2016.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5124536/

4) Framework for FDA's Real World Evidence Program
FDA. 2018.
https://www.fda.gov/media/120060/download

Helpful Explanation

1) RWE for Regulatory Decision Making: List of Expert Documents and Resources on RWE from the International Society for Pharmacoepidemiology (ISPE)
International Society for Pharmacoepidemiology. Last accessed January 20, 2022.
https://www.pharmacoepi.org/strategic-initiatives/rwe-for-regulatory-decision-making/

2) An Inventory of European Data Sources for the Long-Term Safety Evaluation of Methylphenidate
Murray ML, Insuk S, Banaschewski T, Neubert AC, McCarthy S, et al. *Eur Child Adolesc Psychiatry*. 2013.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830128/

3) Causal Models and Learning from Data: Integrating Causal Modeling and Statistical Estimation
Petersen ML, van der Laan MJ. *Epidemiology*. 2014.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4077670/

4) Development of a Neonatal Adverse Event Severity Scale Through a Delphi Consensus Approach
Salaets T, Turner MA, Short M, Ward RM, Hokuto I, et al; International Neonatal Consortium. *Arch Dis Child*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943241/

5) Assessment of Long-Term Neurodevelopmental Outcome Following Trials of Medicinal Products in Newborn Infants
Marlow N, Doyle LW, Anderson P, Johnson S, Bhatt-Mehta V, et al; International Neonatal Consortium (INC). *Pediatr Res*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848023/

6) New-User and Prevalent-User Designs and the Definition of Study Time Origin in Pharmacoepidemiology: A Review of Reporting Practices
Luijken K, Spekreijse JJ, van Smeden M, Gardarsdottir H, Groenwold RHH. *Pharmacoepidemiol Drug Saf*. 2021.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8252086/

7) Pharmacoepidemiological Safety Studies in Children: A Systematic Review
Osokogu OU, Dukanovic J, Ferrajolo C, Dodd C, Pacurariu AC, et al. *Pharmacoepidemiol Drug Saf*. 2016.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5111763/

8) Gene Therapy in Rare Diseases: The Benefits and Challenges of Developing a Patient-Centric Registry for Strimvelis in ADA-SCID.
Stirnadel-Farrant H, Kudari M, Garman N, Imrie J, Chopra B, et al. *Orphanet J Rare Dis*. 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889583/

9) Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies
FDA. 2012.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-reporting-requirements-inds-investigational-new-drug-applications-and-babe

10) Rare Diseases: Natural History Studies for Drug Development
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development

11) Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
FDA. 2021.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory?utm_medium=email&utm_source=govdelivery

12) Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions.
FDA. 2022
https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Additional Resources

Public

1) World Federation of Hemophilia Gene Therapy Registry
Konkle BA, Coffin D, Pierce GF, Clark C, George L, et al; Members of the WFH Gene Therapy Registery Steering Committee. *Haemophilia*. 2020.
https://onlinelibrary.wiley.com/doi/10.1111/hae.14015

2) Recommendations for the Design of Therapeutic Trials for Neonatal Seizures
Soul JS, Pressler R, Allen M, Boylan G, Rabe H, et al; International Neonatal Consortium. *Pediatr Res*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760680/

3) Development of a Retinopathy of Prematurity Activity Scale and Clinical Outcome Measures for Use in Clinical Trials
Smith LEH, Hellström A, Stahl A, Fielder A, Chambers W, et al; Retinopathy of Prematurity Workgroup of the International Neonatal Consortium. *JAMA Ophthalmol*. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6565513/

4) Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available
Hernán MA, Robins JM. *Am J Epidemiol*. 2016.
https://academic.oup.com/aje/article/183/8/758/1739860

Not Public

5) Pediatric Post-Marketing Safety Systems in North America: Assessment of the Current Status
McMahon AW, Wharton GT, Bonnel R, DeCelle M, Swank K, Testoni D, Cope JU, Smith PB, Wu E, Murphy MD. *Pharmacoepidemiol Drug Saf*. 2015
https://pubmed.ncbi.nlm.nih.gov/26098297/

6) Research on the Effects of Medications in Pregnancy and in Children. In "Pharmacoepidemiology, Sixth Edition."
Horton DB, Hernandez-Diaz S, Lasky T, Huybrechts KF. *Wiley*. 2019. Chapter 22, pp. 524-560
https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119413431.ch22

7) Pharmacoepidemiology: A Time for a New Multidisciplinary Approach to Precision Medicine
Issa AM, Carleton B, Gerhard T, Filipski KK, Freedman AN, et al. *Pharmacoepidemiol Drug Saf*. 2021.
https://pubmed.ncbi.nlm.nih.gov/33715268/

8) Review of the Methods to Obtain Paediatric Drug Safety Information: Spontaneous Reporting and Healthcare Databases, Active Surveillance Programmes, Systematic Reviews and Meta-Analyses
Gentili M, Pozzi M, Peeters G, Radice S, Carnovale C. *Curr Clin Pharmacol*. 2018.
https://pubmed.ncbi.nlm.nih.gov/29412117/

9) Pharmacoepidemiological Research for the Development and Evaluation of Drugs in Pediatrics
Kaguelidou F, Durrieu G, Clavenna A. *Therapie*.
https://pubmed.ncbi.nlm.nih.gov/30773345/

10) Summary of Literature on Pediatric Real-World Evidence and Effectiveness
McMahon AW, Quinto K, Abernethy A, Corrigan-Curay J. *JAMA Pediatr*. 2021.
https://jamanetwork.com/journals/jamapediatrics/article-abstract/2782029

How PK Modeling Can be Used to Inform Dosing

Read this First

1) A Pharmacokinetic Standard for Babies and Adults
Holford N, Heo YA, Anderson B. *J Pharmaceutical Sciences*. 2013.
https://jpharmsci.org/article/S0022-3549(15)30935-7/fulltext

2) Physiologically-Based Pharmacokinetic Models for Children: Starting to Reach Maturation?
Verscheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM. *Pharmacol Ther.* 2020.
https://www.sciencedirect.com/science/article/pii/S0163725820300693?via%3Dihub

3) Physiologically Based Pharmacokinetic Modeling and Simulation in Pediatric Drug Development
Maharaj AR, Edginton AN. *CPT Pharmacometrics Syst. Pharmacol*. 2014.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260000/

4) Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the Optimization of Individualized Dosing Regimens
Stockmann C, Barrett JS, Roberts JK, Sherwin CMT. *CPT Pharmacometrics Syst Pharmacol.* 2015.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716585/

5) General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
FDA. 2014.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products

Helpful Explanation

1) Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007
Momper JD, Mulugeta Y, Green DJ, Karesh A, Krudys KM, et al. *JAMA Pediatr*. 2013.
https://jamanetwork.com/journals/jamapediatrics/fullarticle/1723817

2) Drugs and Lactation Database (LactMed)
NIH/National Library of Medicine. Last accessed January 20, 2022.
https://www.ncbi.nlm.nih.gov/books/NBK501922

3) Brivaracetam Population Pharmacokinetics in Children with Epilepsy Aged 1 Month to 16 Years
Schoemaker R, Wade JR, Stockis A. *Eur J Clin Pharmacol*. 2017.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423986/

4) General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products.
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-neonatal-studies-drugs-and-biological-products-guidance

5) Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls
Abdel-Rahman SM, Reed MD, Wells TG, Kearns GL. *Clin Pharmacol Ther*. 2007.
https://pubmed.ncbi.nlm.nih.gov/17329988/

Additional Resources

1) Scientific Guidelines: Paediatrics
EMA. Last accessed January 20, 2022.
https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/scientific-guidelines-paediatrics

2) Clinical Lactation Studies and the Role of Pharmacokinetic Modeling and Simulation in Predicting Drug Exposures in Breastfed Infants
Anderson PO, Momper JD. *J Pharmacokinet Pharmacodyn*. 2020.
https://pubmed.ncbi.nlm.nih.gov/32034606/

3) The Integration of Allometry and Virtual Populations to Predict Clearance and Clearance Variability in Pediatric Populations over the Age of 6 Years
Edginton AN, Shah B, Sevestre M, Momper JD. *Clin Pharmacokinet*. 2013.
https://pubmed.ncbi.nlm.nih.gov/23588537/

The Role of Quantitative Systems Pharmacology in PDD

Read This First

1) Quantitative and Systems Pharmacology in the Post-Genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms. *An NIH White Paper by the QSP Workshop Group*
Rebecca Ward, editor. *NIGMS*. 2011.
https://www.nigms.nih.gov/training/documents/systemspharmawpsorger2011.pdf

2) History and Future Perspectives on the Discipline of Quantitative Systems Pharmacology Modeling and Its Applications
Azer K, Kaddi CD, Barrett JS, Bai JPF, McQuade ST, et al. *Front Physiol*. 2021.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027332/

3) A Six-Stage Workflow for Robust Application of Systems Pharmacology
Gadkar K, Kirouac DC, Mager DE, van der Graaf PH, Ramanujan S. *CPT Pharmacometrics Syst Pharmacol.* 2016.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879472/

4) Systems Pharmacology
Boran AD, Iyengar R. *Mt Sinai J Med*. 2010.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113679/

5) Predictive Pediatric Modeling and Simulation Using Ontogeny Information
Ince I, Solodenko J, Frechen S, Dallmann A, Niederalt C, et al. *J Clin Pharmacol*. 2019.
https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.1497

6) The Future of Drug Development: The Paradigm Shift Towards Systems Therapeutics
Danhof M, Klein K, Stolk P, Aitken M, Leufkens H. *Drug Discov Today*. 2018.
https://www.sciencedirect.com/science/article/pii/S1359644618302551?via%3Dihub

Helpful Explanation

1) The Systems Biology of Drug Metabolizing Enzymes and Transporters: Relevance to Quantitative Systems Pharmacology
Nigam SK, Bush KT, Bhatnagar V, Poloyac SM, Momper JD. *Clin Pharmacol Ther*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292762/

2) Approaches to Dose Finding in Neonates, Illustrating the Variability between Neonatal Drug Development Programs
Van den Anker JN, McCune S, Annaert P, Baer GR, Mulugeta Y, et al. *Pharmaceutics*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7408157/

3) Pharmacometrics and Systems Pharmacology for Metabolic Bone Diseases
Riggs MM, Cremers S. Br J Clin Pharmacol. 2019.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533428/

4) Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa is an Innovative Tool for Linking Pathophysiology and Pharmacology
Kaddi CD, Niesner B, Baek R, Jasper P, Pappas J, et al. *CPT Pharmacometrics Syst Pharmacol.* 2018.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6063739/

5) Transitioning from Basic toward Systems Pharmacodynamic Models: Lessons from Corticosteroids
Ayyar VS, Jusko WJ. *Pharmacol Rev*. 2020.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7058984/

6) How Does In Vivo Biliary Elimination of Drugs Change with Age? Evidence from In Vitro and Clinical Data Using a Systems Pharmacology Approach
Johnson TN, Jamei M, Rowland-Yeo K. *Drug Metab Dispos.* 2016.
https://dmd.aspetjournals.org/content/44/7/1090.long

Additional Resources

1) A Survey of Neonatal Pharmacokinetic and Pharmacodynamic Studies in Pediatric Drug Development
Wang J, Avant D, Green D, Seo S, Fisher J, et al. *Clin Pharmacol Ther*. 2015.
https://pubmed.ncbi.nlm.nih.gov/25975723/

2) Exposure-Response Assessment in Pediatric Drug Development Studies Submitted to the US Food and Drug Administration
Zhang Y, Wang Y, Khurana M, Sachs HC, Zhu H, et al. *Clin Pharmacol Ther*. 2020.
https://pubmed.ncbi.nlm.nih.gov/32030741/

3) Failed Pediatric Drug Development Trials
Momper JD, Mulugeta Y, Burckart GJ. *Clin Pharmacol Ther.* 2015.
https://pubmed.ncbi.nlm.nih.gov/25963725/

4) Quantitative Systems Pharmacology: A Promising Approach for Translational Pharmacology
Gadkar K, Kirouac D, Parrott N, Ramanujan S. *Drug Discov Today Technol*. 2016.
https://pubmed.ncbi.nlm.nih.gov/27978989/

5) Translational Quantitative Systems Pharmacology in Drug Development: from Current Landscape to Good Practices
Bai JPF, Earp JC, Pillai VC. *AAPS J*. 2019.
https://pubmed.ncbi.nlm.nih.gov/31161268/