

Methodological and Ethical Issues in Pediatric Medication Safety Research

Delesha Carpenter, PhD, MSPH,^a Daniel Gonzalez, PharmD, PhD,^b George Retsch-Bogart, MD,^{c,d,e} Betsy Sleath, PhD,^a Benjamin Wilfond, MD^f

In May 2016, the Eshelman School of Pharmacy at The University of North Carolina at Chapel Hill convened the PharmSci conference to address the topic of “methodological and ethical issues in pediatric medication safety research.” A multidisciplinary group of experts representing a diverse array of perspectives, including those of the US Food and Drug Administration, children’s hospitals, and academia, identified important considerations for pediatric medication safety research and opportunities to advance the field. This executive summary describes current challenges that clinicians and researchers encounter related to pediatric medication safety research and identifies innovative and ethically sound methodologies to address these challenges to improve children’s health. This article addresses 5 areas: (1) pediatric drug development and drug trials; (2) conducting comparative effectiveness research in pediatric populations; (3) child and parent engagement on study teams; (4) improving communication with children and parents; and (5) assessing child-reported outcomes and adverse drug events.

The safe and effective use of medications in pediatric populations is an important and underdeveloped area of health services research. Although federal agencies such as the Agency for Healthcare Research and Quality have identified medication safety as a priority research area and children/adolescents as a priority research population, specific guidance for conducting medication safety research with pediatric populations is lacking. Although this article will focus on the pediatric population, many of the challenges and opportunities discussed are also applicable to other special populations (eg, pregnant women).¹ Pediatric medication safety research warrants greater attention because it is associated with complex challenges, including age-dependent changes in drug disposition and effects,² establishing safe doses for pediatric versus adult patients,^{3,4} the ethical and practical issues associated

with off-label use of medications, and conducting comparative effectiveness research (CER) in pediatric populations.^{5–7} Furthermore, pediatric medication safety is a timely issue that has been at the forefront of the public’s attention because of a firestorm of media coverage regarding the risks and benefits of childhood vaccinations. Coverage of this issue has highlighted the need for better strategies to communicate medication risks and benefits to parents, children, and adolescents.

To address this important area of research, in May 2016, the Eshelman School of Pharmacy at the University of North Carolina (UNC) at Chapel Hill convened 16 experts from a diverse array of disciplines and settings to share insights from their own work about how they are addressing pressing issues in pediatric medication safety research and what they envision as the next steps to move the field forward.

abstract



^aDivision of Pharmaceutical Outcomes and Policy, ^bDivision of Pharmacotherapy and Experimental Therapeutics, ^cDepartment of Pediatrics, School of Medicine, ^dClinical and Translational Research Center of the North Carolina Translational and Clinical Sciences Institute, and ^eCystic Fibrosis Therapeutics Development Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ^fTreuman Katz Center for Pediatric Bioethics, Seattle Children’s Research Institute, University of Washington, Seattle, Washington

Dr Carpenter was the scientific chair for the conference and drafted the initial manuscript; Drs Gonzalez, Sleath, Retsch-Bogart and Wilfond contributed to writing the manuscript and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Delesha Carpenter, PhD, MSPH, Division of Pharmaceutical Outcomes and Policy, One University Heights, CPO 2125, Asheville, NC 28804. E-mail: dmcarpenter@unc.edu

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TABLE 1 Summary of Pediatric Medication Safety Research Challenges and Innovative Solutions to Address These Challenges

Challenge	Potential Solutions
<p>Pediatric drug development and drug trials</p> <ul style="list-style-type: none"> ● Difficulty recruiting patients with disease of interest and across pediatric age continuum ● Limited blood volume in neonates 	<ul style="list-style-type: none"> ● Opportunistic clinical trials that capitalize on routine care procedures ● Master protocols that allow for collection of data for multiple drugs, indications, and/or biomarkers ● Application of pharmacokinetic/pharmacodynamic modeling and simulation methods to optimize clinical trial design ● Sparse sampling and ultralow volume bioanalytical assays to facilitate blood testing
<p>Conducting CER in pediatric populations</p> <ul style="list-style-type: none"> ● Identifying and enrolling children who meet eligibility criteria and who are at various developmental stages ● EMR issues, including inconsistencies in free text data, incomplete or missing data, and limited ability to extract data across EMR vendors, and incomplete longitudinal data 	<ul style="list-style-type: none"> ● Multisite collaborations of hospitals and health systems that agree to share EMR data ● Data harmonization across EMRs that minimizes missing data (CER²)
<p>Child and parent engagement on study teams</p> <ul style="list-style-type: none"> ● Identifying and engaging children and parents who are representative of the clinical population ● Logistical and/or scheduling issues ● Describing research studies to parents and children ● Identifying ways for parents and children to contribute to all aspects of a study 	<ul style="list-style-type: none"> ● Pediatric collaborative care networks ● Involving children and parents in the earliest stages of a study ● Teleconference technologies and scheduling meetings after school or after work to accommodate family schedules ● Break-out groups that allow children and parents to express their priorities/concerns separately
<p>Improving communication with children and parents</p> <ul style="list-style-type: none"> ● Provider discomfort communicating with youth and parents ● Relying on parent, child, or provider reports of communication quality 	<ul style="list-style-type: none"> ● National guidelines about youth-friendly medication communication (You're Welcome; example from United Kingdom) ● Creating youth-friendly physical spaces to enhance communication ● Conducting direct observations of child-parent-provider communication
<p>Assessing child-reported outcomes and ADEs</p> <ul style="list-style-type: none"> ● Caregivers provide proxy report of child's health and functioning even when child is able to provide such reports ● Data on what constitutes "normal" laboratory values and ADEs in youth are lacking 	<ul style="list-style-type: none"> ● Online libraries of validated child-report measures (Pediatric PRO-CTCAE, PROMIS) ● Pharmacovigilance programs to standardize systems to monitor ADEs in clinical care settings

This summary condenses the 16 presentations into 5 overarching areas: (1) pediatric drug development and drug trials; (2) conducting CER in pediatric populations; (3) child and parent engagement on study teams; (4) improving communication with children and parents; and (5) assessing child-reported outcomes and adverse drug events (ADEs). We first describe current challenges in each of these 5 areas and then discuss state-of-the-art

methodologies that could be used to advance future research (Table 1). Short videos summarizing speakers' key points are available at: <http://tinyurl.com/pharmsci2016>.

DRUG DEVELOPMENT AND DRUG TRIALS IN PEDIATRIC POPULATIONS

Current Challenges

Pediatric initiatives in the United States, such as the Best

Pharmaceuticals for Children Act and the Pediatric Research Equity Act, have paved the way for an expansion in pediatric research by encouraging the pharmaceutical industry to perform necessary studies in children and having the National Institutes of Health (NIH) prioritize therapeutic areas and sponsor clinical trials. Unfortunately, for many drugs, there is still inadequate information in the label to guide the safe and effective use of medications in children, particularly in neonates. For example, between 1997 and 2010, a total of 406 pediatric labeling changes were made in the United States and only 24 (6%) of these included new neonatal information; 13 of the 24 labeling changes (54%) were the inclusion of the statement "safety and effectiveness have not been established."⁸

Conducting clinical trials in neonates and children is difficult given that, often, only a limited number of patients with the disease of interest are available, that enrollment of patients across the pediatric age continuum is needed, and that recruitment can be challenging. Early phase trials focused on characterizing the pharmacokinetic and pharmacodynamic properties of a drug in the pediatric population can be difficult to perform because limited blood volume in neonates requires careful consideration of the number and timing of blood samples collected.

State-of-the-Art Methodology

The use of innovative clinical trial designs, sparse sampling to characterize pharmacokinetics, development of ultralow volume bioanalytical assays to facilitate blood testing, national and international research networks to conduct trials collaboratively, and application of advanced quantitative clinical pharmacology methods to optimize trial design and analyze pediatric data are opportunities

to overcome some of the noted challenges to performing drug trials in children. Master protocols that allow for collection of data for multiple drug treatments, indications, and/or biomarkers are an efficient approach to collecting pediatric data. In addition, opportunistic clinical trials that capitalize on routine care procedures and enroll children who are already receiving the drug as a clinical intervention are another efficient approach to data collection in children that minimizes study risks.⁹ However, opportunistic trials have some potential limitations. For example, in the context of characterizing a drug's pharmacokinetics and/or pharmacodynamics, blood sampling in an opportunistic study can be sparse and variable in timing (if timed with routine care laboratory collections). Additionally, because of the heterogeneity of patients enrolled in opportunistic trials, there can be substantial variability in the doses evaluated, the concomitant medications patients are receiving, and the disease status/severity of patients enrolled in the trial. Furthermore, implementation of pragmatic study design elements for expanding pediatric drug evaluation programs could allow collection of comparative effectiveness data for drugs evaluated in a real-world setting. However, there are ethical considerations to performing pragmatic trials postapproval that would need to be addressed, including concerns related to the random assignment of real-world patients and the level of oversight needed for these trials.¹⁰

Pharmacokinetic and/or pharmacodynamic modeling and simulation methods can be used to optimize dose selection in early phase trials to maximize the likelihood that the studied dose will have a beneficial efficacy and safety profile.¹¹ For example, population pharmacokinetic models are often

developed by using sparse samples collected in early phase studies. Enrollment in these studies can occur in a sequential fashion (from the oldest to youngest pediatric age groups), and the model can be updated as additional pediatric data become available. These models can then be used to select the dosing regimen(s) that will be evaluated in follow-up efficacy and safety studies. In addition to aiding with dose selection, developed pharmacokinetic and/or pharmacodynamic models can also be applied to perform clinical trial simulations that can aid in optimizing other study design characteristics (eg, sample size, timing of pharmacokinetic sampling).¹² The use of Bayesian methods, such as Bayesian hierarchical modeling and the derivation of formal previous distributions by using adult data, has also been highlighted by regulators as an approach to increase the likelihood of success of pediatric drug development programs.^{13,14} Although there are ethical issues to consider to ensure that children and families are respected and that risks are minimized, these issues are addressable, and the scientific necessity and social value of conducting such research is in itself an ethical consideration.¹⁵⁻¹⁷

CONDUCTING CER IN PEDIATRIC POPULATIONS

Current Challenges

CER is costly and time-consuming to implement in pediatric populations. Identifying a sufficient number of children who meet eligibility criteria for noninterventional retrospective studies and enrolling enough children to adequately power prospective trials can be difficult within a single site or even across multiple sites, especially for rare conditions. Additionally, because clinically important differences may vary within the pediatric population

(eg, differences between young children and teens), the authors of both retrospective and prospective studies should strive to include sufficient numbers of children at various developmental stages to examine changes in treatment effects.¹⁸ Given that electronic medical record (EMR) use among pediatricians has increased from 58% to 79% in 2012¹⁹ and continues to grow, EMRs offer great potential to overcome the aforementioned barriers to conducting retrospective and prospective CER studies. However, several challenges exist to using EMRs to conduct pediatric CER studies, including inconsistencies in how free text data are documented in various EMR systems, incomplete or missing data across systems, and limited ability to extract data across EMR vendors.²⁰ Limited ability to extract data across EMR vendors is particularly problematic for the authors of prospective studies in which patients may receive care from multiple hospitals or specialty care practices. In these cases, researchers may have incomplete longitudinal data on the types of care received, which can confound study results.²¹

One ethical issue that poses challenges is how to assess the risks and obtain consent in such research that involves standard medical practices. Draft regulatory guidance in 2014 suggested that potential differences in efficacy between standard drugs should be considered risks of research.^{22,23} The problematic implication of this view is that such research would pose more than minimal risk, which would influence the approach to consent. However, there is not agreement about calling this a research risk. An alternative perspective is that these are clinical risks and not research risks. The impact of drug selection is a clinical risk related to choosing one drug or another drug.²⁴ This information should be conveyed to potential research participants, but

the risk is from the choice of drug and not from the decision to enroll in the study. This issue has not been resolved, and different institutional review boards have different approaches.²⁵

State-of-the-Art Methodology

Multisite collaborations of hospitals and health systems that agree to share EMR data on child outcomes offer unprecedented opportunities to study the effectiveness of medications and surgical procedures in pediatric populations. For example, the PEDSnet clinical data research network is a consortium of multiple children's hospitals, 2 patient-centered, disease-specific pediatric networks, a pediatric obesity network, and 2 national data partners.²⁶ Data collected as part of this consortium can be used for continuous monitoring of outcomes and CER. In 1 case, data from several of these multisite collaborations have been combined to create an über-network of child health data. This über-network is referred to as the Comparative Effectiveness Research through Collaborative Electronic Reporting (CER²).²⁷ Currently, the CER² database has more than 14 years of longitudinal data on over 1.2 million children seen by over 2000 practitioners at 222 practice sites across the United States. The database allows for retrospective studies and can also support participant recruitment for prospective studies. The data are harmonized across different sites, allowing researchers quick access to a database that contains clinical information and samples large enough to study rare events. Importantly, the research team has been able to effectively address methodological issues related to missing data on race and ethnicity, and the data set includes children of all ages, allowing researchers to take a life-course perspective on treatment effectiveness and child outcomes. Even with databases of this size, recruiting enough patients

with certain rare diseases or rare events could still be difficult, although new studies are emerging that reveal that large databases, such as the one described above, are able to overcome this. For example, as recently reported at the Pediatric Academic Societies conference, CER² has been used to successfully study rare medication-related events.²⁸ Specifically, researchers were able to estimate the risk of an arrhythmia (a rare event) associated with short-term β agonist use in pediatric patients with asthma and determine the difference in risk related to on- versus off-label status. Insurance claims data can also be used to compare medication outcomes for pediatric patients on a national level, but claims data can be limited depending on how many children are enrolled in a particular plan and may not link all prescription claims to hospital claims.

Additionally, although it is possible to “waive” regulatory consent for research that just uses medical records, some data suggest that the public is just as interested in giving consent for this type of research.^{29,30} Regulatory consent refers to the formalized approach with a detailed informed consent document. When a study is minimal risk, the institutional review board can not only waive consent but also approve an “altered” approach, such as an information sheet given to a patient in person or delivered to a patient by mail or Web site notification. Such approaches may address ethical issues, such as respect and transparency, and also have the potential to improve community support for this critical research.

CHILD AND PARENT ENGAGEMENT ON STUDY TEAMS

Current Challenges

In recent years, the importance of engaging children and parents on study teams has been emphasized, most notably by the Patient

Centered Outcomes Research Institute. Although many clinicians and researchers recognize the importance of incorporating child and parent perspectives into the research process, many are unsure of the most effective ways to do this. Research is beginning to emerge on strategies to engage patients on study teams, but fewer study authors have focused on pediatric populations.³¹ Researchers have struggled with several issues, including identifying children and parents who are representative of their clinical population and also willing and able to participate on study teams, overcoming logistical issues related to scheduling team meetings, effectively describing research studies to parents and children, and identifying ways for parents and children to contribute to all aspects of a study, including data analysis and dissemination.

State-of-the-Art Methodology

Pediatric collaborative care networks offer a national structure within which to meaningfully engage families, researchers, providers, and other stakeholders to develop research agendas that address the issues that are of greatest concern to children, parents, and providers.³² Pediatric collaborative care networks, which include patient-powered research networks, are networks of patient organizations focused on a particular health condition that are interested in sharing health information to design and implement CER studies and improve the quality of health care.³³ Currently, several pediatric collaborative networks exist, including networks for the subspecialties of cardiology, gastroenterology, and rheumatology.³⁴ Within these networks, teams of stakeholders, including children and their parents, meet frequently to help health care organizations understand how they

can improve their care and identify priority areas for research studies.

A critical factor related to the success of these networks is involving children and parents in the earliest stages of study, including research question development. As a group, child, parent, and provider stakeholders are then continually engaged throughout the research process, including dissemination of study findings. These networks are often facilitated by teleconference technologies that allow national groups of parents, children, and providers to meet frequently without the need for travel. Team meetings often take place after school or work to accommodate family schedules, and breakout groups that allow children and parents to express their priorities and concerns separately ensure that the voices of both children and their parents are heard. Developing and sustaining collaborative care networks requires the investment of financial resources, including dedication of staff time to schedule meetings, which can make them more difficult to implement in smaller health care organizations. These network models have had great success at improving pediatric outcomes. For example, since the implementation of the ImproveCareNow network, which includes 87 gastrointestinal centers and 25 000 pediatric Crohn disease and ulcerative colitis patients, the rates of inactive disease have significantly increased by ~12%.³⁵ Such approaches to community engagement can address the ethical concerns of families and communities but also require that these groups themselves consider the ethical issues related to design and recruitment within the community.^{36,37}

IMPROVING COMMUNICATION WITH CHILDREN AND PARENTS

Current Challenges

Despite evidence that communicating directly with children leads to

improved health behaviors and clinical outcomes,^{38,39} provider communication about medications and treatment options with youth and parents in clinical settings, such as pediatric practices and pharmacies, remains suboptimal. For example, community pharmacists only counsel children about their medications 2% of the time.⁴⁰ Opportunities for pharmacists to engage children in pertinent medication and health-related discussions may also be limited by state laws. For example, 39% of states do not allow pharmacists to administer human papillomavirus vaccinations.⁴¹ Moreover, providers may often feel uncomfortable or unprepared when communicating with youth and parents. Methodological limitations involve relying on parent and child reports of communication rather than direct observation of interactions, which can be problematic because of providers' overestimation of how often they engage youth in health-related discussions.⁴⁰ Potential improvements to communication are not limited to in-person interactions, as communication via electronic modalities (eg, text message, e-mail) and better labeling of prescription drugs are also needed to ensure patient comprehension.

State-of-the-Art Methodology

Improving provider communication with youth could be facilitated by a set of national guidelines designed to help providers address the multilevel factors that influence quality of communication about medications. For example, the United Kingdom has the You're Welcome criteria,⁴² which constitute a framework that identifies 10 factors for facilitating youth-friendly communication; the United States does not have a similar framework to promote effective youth-centered communication in clinical settings. Once developed, guidance on how to put these

guidelines into practice in various clinical settings would be needed and would include addressing the specific factors that negatively affect providers' confidence in communicating with youth about particular medications or health issues in pharmacies versus clinics, for example. The physical environment is often neglected when considering facilitators of child-provider communication. Thus, innovative opportunities exist to create physical spaces that are conducive to child-provider communication (eg, private, kid-friendly, and aesthetically pleasing spaces). Additionally, the methodological rigor of communication studies can be improved by conducting direct observational studies of youth-provider communication rather than relying on parent, child, and provider self-report of the quality of communication.

ASSESSMENT OF CHILD-REPORTED OUTCOMES AND ADES

Current Challenges

Caregivers are often responsible for providing information on the symptomology and quality of life of infants and young children. However, despite evidence that children as young as 8 years of age can validly and reliably report their health status, researchers and clinicians frequently continue to ask caregivers to provide proxy reports of children's functioning and health status.⁴³ This practice is problematic given that children's reports of their health and functioning are only weakly to moderately correlated with caregiver and clinician reports, leading to inaccurate estimates of how disease impacts children's lives.^{44,45} Clinicians' and researchers' ability to accurately report ADEs for children of different ages is complicated by the fact that data on what constitutes "normal" laboratory

values in pediatric populations are often lacking. Inaccurate reporting of ADEs can lead providers to prescribe contraindicated medications or choose suboptimal treatments.

State-of-the-Art Methodology

Online libraries of validated measures are currently being developed for clinicians and researchers to use with pediatric patients to assess children's experiences with symptomatic adverse events. One such system, the Pediatric Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (Pediatric PRO-CTCAE) was designed for children and adolescents to self-report symptomatic adverse events experienced while undergoing treatments.⁴⁶ The Pediatric PRO-CTCAE can capture up to 62 adverse events, includes self-report and proxy measures, and is currently being evaluated in prospective observational and interventional studies with children and adolescents with cancer and other chronic diseases. Additionally, work with pharmacovigilance programs has been implemented to standardize systems to monitor ADEs in clinical care settings. These systems ideally include documentation of the type, severity, causality, and avoidability of the ADE for reporting to regulatory agencies. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) also has developed measures to assess child-reported symptoms and health-related quality of life across many chronic conditions (www.nihpromis.com/). Some examples of validated child-reported PROMIS measures include fatigue, depressive symptoms, family relationships, asthma impact, and psychological stress. Additionally, PROMIS has also developed

validated caregiver proxy-report measures for use with caregivers of children ages 5 to 17. Although most of these measures are brief, additional implementation studies may be needed to determine how to most effectively integrate them into provider workflows.

CONCLUSIONS

Thanks to advances in multisite collaborations (eg, PEDSnet and CER²) and health information technology (eg, improved ability to link and analyze free-text EMR data and minimize missing data), an unprecedented opportunity now exists to improve pediatric health outcomes through the development and implementation of ethical and methodologically rigorous large-scale research studies. Use of innovative clinical trial designs, such as opportunistic trials and master protocols, enables researchers, in collaboration with parents, children, and clinicians, to make significant advances in drug development, identifying optimal dosing for medications, as well as conducting studies to identify the best treatment options across the pediatric life-course. By effectively engaging children and parents on study teams throughout the research process, researchers also will ensure that the outcomes studied are relevant to children and their families. Innovations in measure development, including Pediatric PRO-CTCAE and PROMIS, have also allowed us to more accurately capture child-reported outcomes, which can be integrated as endpoints in comparative effectiveness studies. Lastly, conducting more rigorous observational studies of child-parent-provider communication that include direct observation of health care encounters will ensure that providers convey information about treatment

options in ways that children and parents understand, so that they can make informed decisions.

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Hill, NC); Carole Lannon, MD, MPH, Director, Learning Networks Core Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Professor of Pediatrics, University of Cincinnati (Cincinnati, OH); Oksana Pyzik, MPharm, School of Pharmacy, University College London (London, United Kingdom); Bryce B. Reeve, PhD, Health Policy and Management, Lineberger Comprehensive Cancer Center, UNC-Chapel Hill (Chapel Hill, NC); Brian Smith, MD, MPH, MHS, Department of Pediatrics, Division of Neonatal-Perinatal Medicine, Duke University Medical Center, Duke Clinical Research Institute (Durham, NC); David Wohl, MD, School of Medicine, UNC-Chapel Hill, Codirector of HIV Services, North Carolina Department of Corrections (Chapel Hill, NC).

ABBREVIATIONS

ADE: adverse drug event
 CER: comparative effectiveness research
 CER²: Comparative Effectiveness Research through Collaborative Electronic Reporting
 EMR: electronic medical record
 NIH: National Institutes of Health
 PRO-CTCAE: Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events
 PROMIS: Patient-Reported Outcomes Measurement Information System
 UNC: University of North Carolina

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