Published in final edited form as:

Contemp Clin Trials. 2016 March ; 47: 376–382. doi:10.1016/j.cct.2016.03.002.

Optimizing operational efficiencies in early phase trials: the Pediatric Trials Network experience

Amanda England, MD, MPH[a,1], **Kelly Wade, MD, PhD, MSCE**[b], **P. Brian Smith, MD, MPH, MHS**[c,d], **Katherine Berezny, MPH**[d], **Matthew Laughon, MD, MPH**[a], and **on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee**

[a]Division of Neonatal-Perinatal Medicine, The University of North Carolina at Chapel Hill, N.C. Memorial Hospital, 101 Manning Drive, CB# 7596, Chapel Hill, NC 27599-7596, USA

[b]Division of Neonatology, Children's Hospital of Pennsylvania, CHOP Newborn Care at the Hospital of the University of Pennsylvania, 800 Spruce St., Philadelphia, PA 19107, USA

[c]Department of Pediatrics, Duke University School of Medicine, Durham, NC 27710, USA

[d]Duke Clinical Research Institute, Duke University School of Medicine, P.O. Box 17969, Durham, NC 27715, USA

Abstract

Performing drug trials in pediatrics is challenging. In support of the Best Pharmaceuticals for Children Act, the Eunice Kennedy Shriver National Institute of Child Health and Human Development funded the formation of the Pediatric Trials Network (PTN) in 2010. Since its inception, the PTN has developed strategies to increase both efficiency and safety of pediatric drug trials. Through use of innovative techniques such as sparse and scavenged blood sampling as well as opportunistic study design, participation in trials has grown. The PTN has also strived to improve consistency of adverse event reporting in neonatal drug trials through the development of a standardized adverse event table. We review how the PTN is optimizing operational efficiencies in pediatric drug trials to increase the safety of drugs in children.

Keywords

pediatric drug trials; adverse events; organizational improvements

1. Introduction

Performing drug trials in infants and children is challenging. Barriers include low circulating blood volumes, developmental changes in drug-handling systems, perceived risk by

Corresponding author: Matthew Laughon, MD, MPH, Room N4051, N.C. Memorial Hospital, 101 Manning Drive, CB# 7596, Chapel Hill, NC 27599-7596, USA. Phone: (919) 966-5063. matt_laughon@med.unc.edu.

[1]Present address: Ochsner Health System, Section of Neonatology, Ochsner Baptist, 2700 Napoleon Ave., New Orleans, LA 70115, USA

providers and parents, and low parental consent rates. Optimizing enrollment and increasing operational efficiency is critical for on-time, within-budget drug trials in children.

Several drugs used in children are prescribed “off-label” according to regulatory requirements of the Food and Drug Administration (FDA). “Off-label” means that the dose, the population treated, the duration of treatment, or the efficacy has not been established. For example, caffeine citrate is labeled for use in infants 28-33 weeks’ gestational age at birth for the short-term (≤10 days) treatment of apnea of prematurity. Using caffeine in lower gestational age groups (i.e., <28 weeks’ gestation) is considered off-label. The FDA requires that a drug show both safety and efficacy in a specific population at the correct dose before approval for clinical use. This information is then included in the drug label. Due to underrepresentation of pediatric patients in initial drug trials, few drugs are specifically labeled for children (A). The American Academy of Pediatrics identified this problem as far back as 1977 when it stated that the system was unethical because it forced physicians to perform an uncontrolled experiment every time they wrote a prescription [1].

To address this inequality in drug research for children, the U.S. government has passed several pieces of legislation in recent years. The Pediatric Research Equity Act (PREA) requires that most new drugs include children in their studies if there is potential for the drug to be used in the pediatric population. The Best Pharmaceuticals for Children Act (BPCA), passed in 2002, works in conjunction with PREA and allows an additional six months of market exclusivity if the sponsor includes pediatric studies. In addition, the BPCA directed the National Institutes of Health (NIH) to develop a program to improve pediatric drug development, so the Director of the NIH directed responsibility to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to establish pediatric drug development activities [2]. These efforts ultimately led to the creation of the NICHD Pediatric Trials Network (PTN; http://pediatrictrials.org/) in 2010. The PREA and BPCA together have resulted in more than 500 pediatric drug label changes [2].

The PTN is a coalition of research sites located primarily in the United States that collaborate to design and conduct pediatric drug trials, and to help fulfill the legislated requirements of the BPCA (B). Since its inception, the PTN has completed 11 clinical trials, submitted data to the FDA for six different products, enrolled approximately 4,300 patients, and has several projects currently under way (see Table 1) (B). Through experience gained, the investigators and staff of the PTN have overcome challenges in conducting multi-site large pediatric drug trials and worked to optimize operations. We present our collective experience in optimizing operational efficiencies in pediatric drug trials while improving safety.

2. Solutions to Pediatric Research Obstacles

2.1. Optimizing sampling

Drug trials in the pediatric population are challenging due to several factors. One problem is the number and volume of blood samples required for pharmacokinetic (PK) studies. In adults, PK studies traditionally require up to 15 blood samples and relatively high (3 mL) sample volumes [3]. However, children, especially neonates (infants up to 28 postnatal

days), have limited blood volume, and taking a large number or volume of samples is not realistic or safe (e.g., a premature infant weighing 500 g may have a circulating blood volume of only 40-50 mL). Parents are reluctant to allow their children to undergo additional venipunctures or arterial sticks to obtain the blood for these studies.

To address these problems, the PTN has developed techniques that minimize the blood volume and number of additional sticks needed for PK studies. The first technique, sparse sampling, entails population PK modeling to decrease traditional PK study sampling by using only two to three blood draws per patient. Another advantage offered by this method of sampling is flexibility in timing for acquiring samples, as staff can cluster the blood samples with routine care or samples obtained for the other studies. The second method, scavenged sampling, relies on using remaining blood or plasma after laboratory tests for clinical care have been performed on the sample. By performing PK studies on the residual sample, investigators gather information without subjecting the child to any extra punctures or any extra blood loss [4]. The final technique, opportunistic sampling, is used by the PTN whenever possible. This technique requires taking extra fluid at the time of routine sampling. Most of the sticks can be obtained during times of routine blood draws or during times of clinically indicated cerebrospinal fluid sampling. Investigators in the PTN have published several studies using sparse, scavenged, and opportunistic blood samples, and this work has led to increased knowledge of safer antimicrobial doses in neonates [5-10].

To further reduce sample volume, the PTN has used dried blood spot (DBS) sampling. DBS sampling involves ultra-low sample volumes (15-30 μL) collected in a manner similar to newborn metabolic screening tests. Only a few drops of whole blood are placed on blotting paper. This sampling technique requires a very small blood volume, minimal staff training, and easy storage and transport of samples [4]. DBS sampling is a relative newcomer in the field of PK studies, but its use is increasing with both pharmaceutical companies and clinical researchers [11]. In addition, DBS sampling is optimal for neonatal studies because nurses are familiar with blotting whole blood on paper for state newborn screening programs. Since the development of DBS technology, the PTN has published two studies demonstrating effective dosing strategies based on postmenstrual age using DBS [12,13].

An evolving technique is the use of multiple-drug assays that allow researchers to detect levels of more than one drug by using liquid chromatography and mass spectrometry in ultra-low-volume plasma samples [4]. Because most neonates are treated with more than one drug at a single point in time, this technique holds great potential value.

2.2. Maximizing enrollment

Another strategy developed by the PTN to increase drug study participation is called opportunistic design. In this study design, researchers approach parents of children who are already receiving a drug off-label as part of standard-of-care treatment and obtain informed consent to collect samples for PK data. As noted above, since most drugs used in children are off-label (i.e., a different dose, duration, or indication than listed on the FDA label), those drugs are available for the PTN to study. Wade et al. demonstrated the viability of this study design when they examined fluconazole dosing in premature infants [14]. The investigators gathered PK samples when clinicians used fluconazole as part of their local

standard-of-care guidelines. Wade et al. established that most published references for fluconazole dosing in this vulnerable population were suboptimal. The group found that for the treatment of invasive candidiasis in young infants, a dose of 12 mg/kg/day is needed. The previous dosing range recommended a range of 3-12 mg/kg/day, which means some infants were being undertreated [14].

The PTN Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care (POPS) study (ClinicalTrials.gov Identifier: NCT01431326) is an example of an opportunistic study that also uses opportunistic sampling (C). This study includes drugs from the BPCA priority list and enrolls children from different age groups into gaps identified by review of the current FDA label and the medical literature. To date, the POPS study has enrolled more than 1,200 participants across more than 38 sites receiving approximately 35 different drugs. These data have been used to augment data from PK trials (e.g., rifampin, clindamycin) and to design phase 2 trials (e.g., the Antibiotic Safety in Infants With Complicated Intra-Abdominal Infections [SCAMP] trial, examining metronidazole, piperacillin-tazobactam, clindamycin, and gentamicin; ClinicalTrials.gov Identifier: NCT01994993). A disadvantage to these data is that there are limited (if any) safety data and no efficacy data because the study is only designed to characterize the pharmacokinetics of the medications, not to evaluate medication side effects or effectiveness.

The PTN has also broadened inclusion and limited exclusion criteria for phase 1 and 2 studies. During typical study design, researchers establish inclusion and exclusion criteria to establish the optimal study population. For phase 1 and 2 studies, the primary endpoint is generally PK or safety rather than a clinically important endpoint as for a phase 3. In late-phase trials, it is critical to include only participants who might benefit and exclude individuals who might have conditions that would cloud the primary endpoint, and generally these criteria are extensive. However, those designing phase 1 and 2 studies often have the same approach as phase 3 trials, which results in a narrow population for these studies (Table 2). Due to these stringent requirements, few patients may actually qualify as participants. The PTN has worked to broaden inclusion criteria and reduce exclusion criteria for early-phase trials, thus increasing the number of eligible patients. An example is the Pharmacokinetics of Sildenafil in Premature Infants study (ClinicalTrials.gov Identifier: NCT01670136) (D). The study includes infants <365 days of age who are currently receiving sildenafil as part of their clinical treatment (Cohort 1) and infants of gestational age <28 weeks requiring respiratory support (Cohort 2) (Table 2). The exclusion criteria for the study have been minimized to capture the largest possible number of participants while maintaining the safety of the participants.

Another innovative approach to increasing study participation (while also saving time and improving efficiency) is combining multiple drugs in one study. By including multiple drugs in one study design, investigators need to submit only one Institutional Review Board application, develop one protocol, and participate in one research conference call per week. The POPS study is an example of this innovation—by including over 35 drugs in a single study, efficiency is significantly increased. A further example of a study currently under way to determine appropriate dosing and safety of drugs used in neonates is the

Pharmacokinetics of Antistaphylococcal Antibiotics in Infants (Staph Trio) study (ClinicalTrials.gov Identifier: NCT01728363). This study is examining the PK properties of three drugs: rifampin, clindamycin, and ticarcillin-clavulanate in term and premature infants (E). Again, by combining multiple drugs in one study protocol, more data are obtained in an expedited manner.

An additional approach used by the PTN to increase study participation is the concept of empiric, or "add-on," therapy. Some antimicrobials may rarely be used at a particular institution, but thousands of infants at institutions across the United States are exposed each year to those drugs. Using an opportunistic study design to gather data on such drugs would require hundreds of sites for multiple years for a single drug and thus would be impractical. Becausea child cannot ethically be enrolled in a drug trial as a "healthy volunteer" but must have or be at risk of developing a disease to participate in the trial,. Empiric therapy is when researchers add an additional drug that might be beneficial to an individual participant to the treatment regimen already established at a particular institution. For example, if an institution traditionally treats necrotizing enterocolitis in infants with oxacillin and gentamicin, researchers can add meropenem to the treatment regimen to gather PK data about that particular drug. In this case, the infant might be infected with a resistant gram-negative rod at the time of the infection and meropenem would be of benefit to the infant. Using add-on therapy, members of the PTN have gained valuable PK information for multiple antimicrobial agents in understudied patient populations [6,8,13,15-19]. In addition to adding valuable information to the literature, the work done by the PTN using add-on therapy has had practical implications. The FDA recently changed the drug label for meropenem [18] (F).

3. Organizational Improvements to Increase Efficiency

The PTN has discovered that study participant recruitment is not the only barrier to pediatric clinical research. The PTN is composed of over 160 individual institutions across the country, each of which has their own organizational boards and governing bodies. As any investigator who has performed a multi-center trial has learned, research contracts take months, sometimes more than a year, to secure approval, depending on the site. In addition, some sites require that a contract is in place before submitting to their local Institutional Review Board or gathering other regulatory documents. To streamline efficiency, the PTN developed a single master service agreement for each site. Once that master contract is approved by a particular research location, each additional study in which that institution participates is added to the master contract as an addendum. This innovation has cut the contract processing time by half, in some cases down to 4 weeks. Furthermore, the time to execute additional study contracts decreases because contracts for further studies are merely added as addendums to the already existing contract.

Another method used by the PTN to increase efficiency is optimal site selection and site management for research studies. Historically, the top quintile of research sites enrolls the majority of patients. The PTN ranks each site prior to site selection with weight placed on previous collaboration with the PTN, past successful recruitment, site investigator experience and enthusiasm, and site coordinator experience. For optimal site management

and to engage sites, a monthly phone call is held so that sites with successful recruitment can share experiences with other sites about recruitment optimization, answer questions, and troubleshoot barriers (such as drug shortages). The PTN distributes a newsletter for every trial that explains how the top sites are recruiting patients and describes their successes. These newsletters usually have examples or cases which illustrate questions that might have been sent to the central study team. The PTN also generates a network-wide newsletter to all participating and potential sites that summarizes progress and results. These newsletters engage current sites and generate interest from new investigators.

For sites that are having trouble with recruiting, the PTN generally takes a stepwise approach. First, a member of the central study staff reviews the screening log and identifies possible barriers. Second, the study protocol principal investigators review possible barriers and solutions with site investigators and staff at underperforming locations to help troubleshoot some of their institutional barriers. And, finally, principal investigators are willing to visit locations with low recruitment to improve organizational buy-in. Experience has shown that these practices can increase enrollment throughout the PTN.

Operational efficiency has been gained through the development of standard working instructions and templates. Individual clinical trial teams tend to have little interaction with other trial teams. The PTN discovered quickly that this “silo” approach would not sustain a large network long-term. Therefore, network-specific processes were created, and all team members were trained in these procedures. Templates were created for repeating documents such as protocols, informed consent forms, and the manual of procedures. Different templates for each step of the study—from Institutional Review Board submissions to data collection forms—allow clinicians to spend more time analyzing data and recruiting patients, and less time completing necessary paperwork. The work instructions and templates provide consistency between the different network trials, which has decreased the time and number of personnel required to operationalize a trial.

By improving organizational efficiency through these various techniques, the PTN has been able to undertake more research projects and produce valuable results. The decreased time from the start of a study to completion decreases both research fatigue and costs. This streamlined approach to organizational operations is key to the PTN’s ongoing success.

4. Safety Across and Within Pediatric Trials

The FDA has defined safety-reporting requirements for drugs (G). Adverse events (AEs), as described by the FDA, are any untoward medical occurrence in any human using the drug. The AE is considered a “suspected AE” if there is any reasonable possibility that the drug caused the AE. Study investigators must also track serious adverse events (SAEs), which are AEs that are life-threatening, cause hospitalization or prolong the current hospitalization, prevent the ability to conduct normal life functions, cause congenital defects, or result in death (G).

Although the FDA has established safety-reporting guidelines, the agency leaves the actual definitions of what qualifies as an AE versus SAE to each individual study sponsor or

investigator. This policy can lead to wide variations between sites and between studies regarding which outcomes are reported to the FDA as SAEs. To provide consistent safety standards across studies while improving efficiency, the PTN has designed a Neonatal Adverse Event Table. This innovative table defines abnormal laboratory values and common clinical entities as either AEs or SAEs (Table 3) [20-39]. By providing consistent definitions, safety events can be compared across sites and across studies. These definitions do not limit site investigators or study staff to these events. For example, if an infant receives a drug and has an event that is not listed, then the site investigator may deem that event an AE or SAE. The AE table also increases efficiency during protocol development, because the study team can use the same table for each protocol.

The first step in composing the reference safety table was identifying a common list of laboratory values and clinical events. We identified laboratory values and clinical events applicable to premature infants from the National Institutes of Health's Division of AIDS and the National Cancer Institute's toxicity tables (H,I). Laboratory values and clinical entities applicable to neonates were pulled from these tables, and premature infant specific events (e.g., intraventricular hemorrhage) were added to the list.

We then divided the laboratory values and clinical events into AEs and SAEs. We performed literature searches in Medline using the terms *premature infant*, *normal value*, *normal range*, and *definition of neonatal x*, with *x* defined as the specific parameter desired. We identified gold standard articles as those that defined the normal range of laboratory values in neonates. For clinical events, we identified gold standard articles as those that defined the point within the disease where outcomes significantly worsened. For laboratory values, an AE was defined as two standard deviations away from the mean of the normal range, and an SAE was defined as three standard deviations away from the mean (Table 3). For clinical entities, an AE was defined as having the actual disease process present, and an SAE was defined at the point where hospital length of stay was prolonged (Table 4) [40-52]. If an article meeting the gold standard could not be found, other studies citing normal ranges were sought. These were identified from articles that were found in the previous search. Once the laboratory values and clinical entities were determined, multiple investigators at different research sites determined whether the values correlated with clinical significance. If an article citing reference ranges or long-term outcomes could not be found, then the AEs and SAEs were decided on by group consensus.

This table is the first tool developed to use the existing literature to design an evidence-based approach to define AE and SAEs. The goal is to standardize safety standards for neonatal drug trials and provide more consistent criteria for AEs and SAEs.

5. Conclusion

The PTN continues to lead the way in the realm of pediatric trials through innovative study design, efficient operations, and improved safety. Our goal is for other research networks and investigators to utilize some of the same productive techniques we have learned over the years. Through innovative study designs, improved safety standards, and efficient

operations, we continue striving to produce accurate pediatric drug information, allowing pediatricians and those who treat children to give evidence-based doses of medications.

Acknowledgments

Funding: This work was funded under Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) contract HHSN275201000003I for the Pediatric Trials Network and under NICHD award number 1R25-HD076475-01. Research reported in this publication was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under award number UL1TR001117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Brian Smith receives salary support for research from the NIH and the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the NICHD (HHSN275201000003I and 1R01-HD081044-01), and the Food and Drug Administration (1R18-FD005292-01). Dr Smith receives research support from Cempra Pharmaceuticals (subaward to HHS0100201300009C) and industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Matthew Laughon is supported by the U.S. government for his work in pediatric and neonatal clinical pharmacology (HHSN267200700051C [Principal Investigator: Benjamin]), the NICHD (K23 HD068497), and the National Heart, Lung, and Blood Institute (R34 HL124038).

Abbreviations

BPCA	Best Pharmaceuticals for Children Act
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
PTN	Pediatric Trials Network

References

1. American Academy of Pediatrics; Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics. 1977; 60(1):91–101. [PubMed: 876741]
2. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, et al. Off-label use of drugs in children. Pediatrics. 2014; 133(3):563–7. [PubMed: 24567009]
3. Sammons H. Ethical issues of clinical trials in children: a European perspective. Arch Dis Child. 2009; 94(6):474–7. [PubMed: 19208673]
4. Laughon MM, Benjamin DK Jr, Capparelli EV, Kearns GL, Berezny K, Paul IM, et al. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol. 2011; 4(5):643–52. [PubMed: 21980319]
5. Wade KC, Wu D, Kaufman DA, Ward RM, Benjamin DK Jr, Sullivan JE, et al. Population pharmacokinetics of fluconazole in young infants. Antimicrob Agents Chemother. 2008; 52(11): 4043–9. [PubMed: 18809946]
6. Benjamin DK Jr, Smith PB, Arrieta A, Castro L, Sanchez PJ, Kaufman D, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. Clin Pharmacol Ther. 2010; 87(1): 93–9. [PubMed: 19890251]
7. Smith PB, Walsh TJ, Hope W, Arrieta A, Takada A, Kovanda LL, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. Pediatr Infect Dis J. 2009; 28(5):412–5. [PubMed: 19319022]
8. Cohen-Wolkowiez M, Ouellet D, Smith PB, James LP, Ross A, Sullivan JE, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. Antimicrob Agents Chemother. 2012; 56(4):1828–37. [PubMed: 22252819]
9. Cohen-Wolkowiez M, Benjamin DK Jr, Piper L, Cheifetz IM, Moran C, Liu P, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. Clin Pharmacol Ther. 2011; 89(5):702–7. [PubMed: 21412233]

10. Cohen-Wolkowiez M, Benjamin DK Jr, Ross A, James LP, Sullivan JE, Walsh MC, et al. Population pharmacokinetics of piperacillin using scavenged samples from preterm infants. Ther Drug Monit. 2012; 34(3):312–9. [PubMed: 22569355]
11. Spooner N, Lad R, Barfield M. Dried blood spots as a sample collection technique for the determination of pharmacokinetics in clinical studies: considerations for the validation of a quantitative bioanalytical method. Anal Chem. 2009; 81(4):1557–63. [PubMed: 19154107]
12. Cohen-Wolkowiez M, Sampson M, Bloom BT, Arrieta A, Wynn JL, Martz K, et al. Determining population and developmental pharmacokinetics of metronidazole using plasma and dried blood spot samples from premature infants. Pediatr Infect Dis J. 2013; 32(9):956–61. [PubMed: 23587979]
13. Cohen-Wolkowiez M, Watt KM, Zhou C, Bloom BT, Poindexter B, Castro L, et al. Developmental pharmacokinetics of piperacillin and tazobactam using plasma and dried blood spots from infants. Antimicrob Agents Chemother. 2014; 58(5):2856–65. [PubMed: 24614369]
14. Wade KC, Benjamin DK Jr, Kaufman DA, Ward RM, Smith PB, Jayaraman B, et al. Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. Pediatr Infect Dis J. 2009; 28(8):717–23. [PubMed: 19593252]
15. Piper L, Smith PB, Hornik CP, Cheifetz IM, Barrett JS, Moorthy G, et al. Fluconazole loading dose pharmacokinetics and safety in infants. Pediatr Infect Dis J. 2011; 30(5):375–8. [PubMed: 21085048]
16. Watt KM, Benjamin DK Jr, Cheifetz IM, Moorthy G, Wade KC, Smith PB, et al. Pharmacokinetics and safety of fluconazole in young infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J. 2012; 31(10):1042–7. [PubMed: 22627870]
17. Cohen-Wolkowiez M, Watt KM, Hornik CP, Benjamin DK Jr, Smith PB. Pharmacokinetics and tolerability of single-dose daptomycin in young infants. Pediatr Infect Dis J. 2012; 31(9):935–7. [PubMed: 22627869]
18. Smith PB, Cohen-Wolkowiez M, Castro LM, Poindexter B, Bidegain M, Weitkamp JH, et al. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J. 2011; 30(10):844–9. [PubMed: 21829139]
19. Sampson MR, Bloom BT, Lenfestey RW, Harper B, Kashuba AD, Anand R, et al. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. Pediatr Infect Dis J. 2014; 33(1):42–9. [PubMed: 24346595]
20. Marcialis MA, Dessi A, Pintus MC, Irmesi R, Fanos V. Neonatal hyponatremia: differential diagnosis and treatment. J Matern Fetal Neonatal Med. 2011; 24(S1):75–79. [PubMed: 21942597]
21. Gawlowski Z, Aladangady N, Coen PG. Hypernatraemia in preterm infants born at less than 27 weeks gestation. J Paediatr Child Health. 2006; 42(12):771–4. [PubMed: 17096711]
22. Goff DA, Higinio V. Hypernatremia. Pediatr Rev. 2009; 30(10):412–3. [PubMed: 19797486]
23. Vemgal P, Ohlsson A. Interventions for non-oliguric hyperkalaemia in preterm neonates. Cochrane Database Syst Rev. 2012; 5:CD005257. [PubMed: 22592703]
24. Loughead JL, Mimouni F, Tsang RC. Serum ionized calcium concentrations in normal neonates. Am J Dis Child. 1988; 142(5):516–8. [PubMed: 3358391]
25. Walker MW, Clark RH, Spitzer AR. Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk. J Perinatol. 2011; 31(3):199–205. [PubMed: 20651693]
26. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011; 127(3):575–9. [PubMed: 21357346]
27. Hays SP, Smith EOB, Sunehag AL. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. Pediatrics. 2006; 118(5):1811–18. [PubMed: 17079549]
28. Victor S, Dickinson H, Turner MA. Plasma aminotransferase concentrations in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2011; 96(2):F144–5. [PubMed: 19574257]
29. Noone D, Kieran E, Molloy EJ. Serum magnesium in the first week of life in extremely low birth weight infants. Neonatology. 2012; 101(4):274–7. [PubMed: 22248691]

30. Weng YH, Chiu YW, Cheng SW, Hsieh MY. Risk assessment for adverse outcome in term and late preterm neonates with bilirubin values of 20 mg/dL or more. Am J Perinatol. 2011; 28(5):405–12. [PubMed: 21365530]
31. Oswari H, Widjaja RK, Rohsiswatmo R, Cleghorn G. Prognostic value of biochemical liver parameters in neonatal sepsis-associated cholestasis. J Paediatr Child Health. 2013; 49(1):E6–11. [PubMed: 23279060]
32. Milcic TL. The complete blood count. Neonatal Netw. 2010; 29(2):109–15. [PubMed: 20211833]
33. Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics. 2009; 123(2):e333–7. [PubMed: 19171584]
34. Del Vecchio A, Motta M. Evidence-based platelet transfusion recommendations in neonates. J Matern Fetal Neonatal Med. 2011; 24(Suppl 1):38–40. [PubMed: 21878062]
35. Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. J Perinatol. 2009; 29(2):130–6. [PubMed: 18818663]
36. Puetz J, Darling G, McCormick KA, Wofford JD. Fresh frozen plasma and recombinant factor VIIa use in neonates. J Pediatr Hematol Oncol. 2009; 31(12):901–6. [PubMed: 19956022]
37. Lorenz JM, Kleinman LI, Markarian K, Oliver M, Fernandez J. Serum anion gap in the differential diagnosis of metabolic acidosis in critically ill newborns. J Pediatr. 1999; 135(6):751–5. [PubMed: 10586180]
38. Soldin SJ, Murthy JN, Agarwalla PK, Ojeifo O, Chea J. Pediatric reference ranges for creatine kinase, CKMB, troponin I, iron, and cortisol. Clin Biochem. 1999; 32(1):77–80. [PubMed: 10074896]
39. Malan AF, Evans A, Heese HD. Serial acid-base determinations in normal premature and full-term infants during the first 72 hours of life. Arch Dis Child. 1965; 40(214):645–50. [PubMed: 5847252]
40. Kessler U, Mungnirandr A, Nelle M, Nimmo AF, Zachariou Z, Berger S. A simple presurgical necrotizing enterocolitis-mortality scoring system. J Perinatol. 2006; 26(12):764–8. [PubMed: 17122786]
41. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978; 187(1):1–7. [PubMed: 413500]
42. Gordon PV, Attridge JT. Understanding clinical literature relevant to spontaneous intestinal perforations. Am J Perinatol. 2009; 26(4):309–16. [PubMed: 19067283]
43. Abend NS, Wusthoff CJ. Neonatal seizures and status epilepticus. J Clin Neurophysiol. 2012; 29(5):441–8. [PubMed: 23027101]
44. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978; 92(4):529–34. [PubMed: 305471]
45. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012; 129(6): 1019–26. [PubMed: 22614775]
46. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004; 144(6):815–20. [PubMed: 15192633]
47. Hegyi T, Anwar M, Carbone MT, Ostfeld B, Hiatt M, Koons A, et al. Blood pressure ranges in premature infants: II. The first week of life. Pediatrics. 1996; 97(3):336–42. [PubMed: 8604266]
48. Schwartz PJ, Stramba-Badiale M. Repolarization abnormalities in the newborn. J Cardiovasc Pharmacol. 2010; 55(6):539–43. [PubMed: 20555231]
49. Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia (SVT). NeoReviews. 2005; 6(7):e339–50.
50. Haas J, Larson E, Ross B, See B, Saiman L. Epidemiology and diagnosis of hospital-acquired conjunctivitis among neonatal intensive care unit patients. Pediatr Infect Dis J. 2005; 24(7):586–9. [PubMed: 15998997]

51. Yelverton JC, Dominguez LM, Chapman DA, Wang S, Pandya A, Dodson KM. Risk factors associated with unilateral hearing loss. JAMA Otolaryngol Head Neck Surg. 2013; 139(1):59–63. [PubMed: 23329092]

52. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117(2):391–7. [PubMed: 16461139]

Web References

A. [Accessed July 20, 2015] Eunice Kennedy Shriver National Institute of Child Health and Human Development. http://bpca.nichd.nih.gov/about/pages/index.aspx

B. [Accessed July 20, 2015] Pediatric Trials Network. http://pediatrictrials.org/

C. [Accessed July 20, 2015] https://clinicaltrials.gov/ct2/show/NCT01431326?term=pops&rank=3

D. [Accessed July 20, 2015] https://www.clinicaltrials.gov/ct2/show/NCT01670136?term=sildenafil&rank=2

E. [Accessed July 20, 2015] https://www.clinicaltrials.gov/ct2/show/NCT01728363?term=Pharmacokinetics+of+antistaphylococcal+antibiotics+in+infants&rank=1

F. [Accessed July 20, 2015] Federal Register. https://www.federalregister.gov/articles/2015/05/28/2015-12848/pediatric-studies-of-meropenem-conducted-in-accordance-with-the-public-health-service-act

G. [Accessed July 20, 2015] Food and Drug Administration. http://www.fda.gov/downloads/Drugs/…/Guidances/UCM227351.pdf

H. Toxicity tables- DMID toxicity tables [Internet]. U.S. Department of Health and Human Services-National Institutes of Health; 2011. http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/pages/toxtables.aspxUpdated December 1, 2011 [Accessed October 2013]

I. Common toxicity criteria manual, version 2.0. National Cancer Institute- CancerTherapy Evaluation Program; 1999. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdfUpdated June 1, 1999 [Accessed July 20, 2015]

Table 1

PTN Trials

Trial	Enrollment	ClinicalTrials.gov ID
Metronidazole PK in infants	24	NCT01222585
Acyclovir PK in infants	32	NCT00491426
TAPE device trial	625	NCT01507090
Hydroxyurea PK	40	NCT01506544
POPS	2100	NCT01431326
Lisinopril PK in children with renal transplants	26	NCT01491919
Staph trio	63	NCT01728363
Sildenafil PK in infants	25	NCT01670136
Clindamycin in obese children	23	NCT01744730
Methadone PK in children	26	NCT01945736
SCAMP	140	NCT01994993
Pantoprazole PK in obese children	41	NCT02186652
Baby TAPE	2000	N/A
Furosemide safety in infants	5	NCT02527798

POPS = Pharmacokinetics of understudied drugs administered to children per standard of care; SCAMP = Safety study of Clindamycin, Ampicillin, Metronidazole, and Piperacillin-tazobactam in infants with complicated intra-abdominal infections.

Table 2

Differences in Inclusion/Exclusion Criteria Between Typical Industry and PTN Trials

Trial	Criteria	
Typical industry	Inclusion	
	•	Written informed consent from parent/guardian
	•	Infant's postnatal age 7-28 days
	•	Gestational age 23-30 weeks
	•	Birth weight 500-1250 g
	•	Receiving mechanical ventilation
	•	F_iO_2 oxygen requirement >0.30, sustained for 30 minutes, to account for suctioning
	•	Chest X-ray consistent with respiratory distress syndrome
	•	EKG normal
	•	Intravenous line in place
	Exclusion	
	•	Infant moribund or likely to die in the next 24-48 hours
	•	Prolonged QT (>500)
	•	Congenital heart defect, except for patent ductus arteriosus, atrial septal defect, or small (<5 mm) ventriculoseptal defect
	•	Pulmonary hypoplasia, congenital diaphragmatic hernia, congenital pulmonary airway malformation, or known congenital genetic surfactant deficiency (e.g., surfactant protein B deficiency)
	•	Chromosomal abnormality (e.g., trisomy 21, 18, or 13)
	•	Congenital CNS malformation (i.e., myelomeningocele, encephalocele, hydrocephalus)
	•	Congenital infectious disease (herpes, toxoplasmosis rubella, syphilis, HIV, etc.)
	•	Positive blood, urine, or CSF culture for pathogen
	•	Necrotizing enterocolitis
	•	Intraventricular hemorrhage with grade 3 or 4
	•	Participation in other clinical trials
	•	Unlikely to follow up (in the opinion of the principal investigator)
	•	Any reason that, in the opinion of the principal investigator, the infant would be ineligible for the trial
PTN - Pharmacokinetics of Sildenafil in Premature Infants (NCT01670136)	Inclusion	
	Cohort 1:	
	•	Gestational age 28 weeks or less receiving sildenafil as standard of care < 365 postnatal days
	Cohort 2:	
	•	Gestational age 28 weeks or less
	•	7-28 postnatal days of age
	•	Mechanical ventilation or nasal continuous positive airway pressure or high-flow nasal cannula
	•	Intravenous line in place
	Exclusion	
	Cohort 1:	

Trial	Criteria	
	•	Any condition that would make the infant, in the opinion of the investigator, unsuitable for the study
	Cohort 2:	
	•	Previous exposure to sildenafil within 7 days prior to enrollment
	•	Any condition that would make the infant, in the opinion of the investigator, unsuitable for the study
	•	History of allergic reactions to sildenafil
	•	AST > upper limit of normal or ALT > 3× upper limit of normal
	•	Currently on a vasopressor for hypotension
	•	Known sickle cell disease

Table 3

Adverse Event Table Laboratory Values

	Adverse Event		Serious Adverse Event	
	Conventional Units	**International System (SI)**	**Conventional Units**	**International System (SI)**
Electrolytes				
Hyponatremia [20]	120–124 mEq/L	120–124 mmol/L	<120 mEq/L	<120 mmol/L
Hypernatremia [21,22]	150–159 mEq/L	150–159 mmol/L	>159 mEq/L	>159 mmol/L
Hypokalemia	2.0–2.5 mEq/L	2.0–2.5 mmol/L	<2.0 mEq/L	<2.0 mmol/L
Hyperkalemia [23]	7–7.9 mEq/L	7.0–7.9 mmol/L	>7.9 mEq/L	>7.9 mmol/L
Bicarbonate: Low	12–14 mEq/L	12–14 mmol/L	<12 mEq/L	<12 mmol/L
Bicarbonate: High	35–45 mEq/L	30–45 mmol/L	>45 mEq/L	>45 mmol/L
Hypocalcemia (ionized) [24]	4.1–4.2 mg/dL	0.7–1.05 mmol/L	<4.1 mg/dL	<0.7 mmol/L
Hypercalcemia (ionized) [24]	5.4–5.7 mg/dL	1.3–1.6 mmol/L	>5.7 mg/dL	>1.6 mmo/L
Renal				
BUN [25]	60–100 mg/dL	21.42–35.7 mmol/L	>100 mg/dL	>35.7 mmol/L
Creatinine [25]	1.5–2.5 mg/dL	132.6–221 μmol/L	>2.5 mg/dL	>221 μmol/L
Endocrine				
Hypoglycemia [26]	25–36 mg/dL	1.4–2 mmol/L	<25 mg/dL	<1.4 mmol/L
Hyperglycemia [27]	250–500 mg/dL	13.9–27.8 mmol/L	>500 mg/dL	>27.8 mmol/L
Gastrointestinal				
Aspartate aminotransferase [28]	200–1000 U/L	3.34–16.7 μkat/L	>1000 U/L	>16.7 μkat/L
Alanine aminotransferase [28]	200–1000 U/L	3.34–16.7 μkat/L	>1000 U/L	>16.7 μkat/L
Alkaline phosphatase [29]	1000–1400 U/L	16.4–23.4 μkat/L	>1400 U/L	>23.4 μkat/L
Conjugated bilirubin [30]	3-10 mg/dL	51.3–171 μmol/L	>10 mg/dL	>171 μmol/L
Gamma-glutamyl transferase [31]	100–125 U/L	1.7–2.1 μkat/L	>125 U/L	>2.1 μkat/L
Hypertriglyceridemia	500–1200 mg/dL	5.7–13.6 mmol/L	>1200 mg/dL	>13.6 mmol/L
Hematologic				
Leukopenia [32]	0.5–2 × 10^3/μL	0.5–2 × 10^9/L	<0.5 × 10^3/μL	<0.5 × 10^9/L
Leukocytosis [32]	30-50 × 10^3/μL	30-50 × 10^9/L	>50 × 10^3/μL	>50 × 10^9/L

	Adverse Event		Serious Adverse Event	
	Conventional Units	**International System (SI)**	**Conventional Units**	**International System (SI)**
Anemia: hemoglobin [33]	7–9 g/dL	70–90 g/L	<7 g/dL	<70 g/L
Anemia: hematocrit [33]	20–26%	0.24–0.26	<20%	<0.24
Polycythemia: hemoglobin [33]	23–24 g/dL	230–240 g/L	>24 g/dL	>240 g/L
Polycythemia: hematocrit [33]	66–70%	0.66–0.7	>70%	> 0.7
Thrombocytopenia [34,35]	50–100 × 10^3/μL	50–100 × 10^9/L	<50 × 10^3/μL	<50 × 10^9/L
Thrombocytosis [35]	450–1000 × 10^3/μL	450–1000 × 10^9/L	>1000 × 10^3/μL	>1000 × 10^9/L
Prothrombin time [36]	18–22 seconds	18–22 seconds	>22 seconds	>22 seconds
Activated partial thromboplastin time [36]	79–101 seconds	79–101 seconds	>101 seconds	>101 seconds
Lactate [37]	45.1–90.1 mg/dL	5–10 mmol/L	>90.1 mg/dL	>10 mmol/L
Musculoskeletal				
Creatine kinase [38]	470–600 U/L	7.9–10 μkat/L	>600 U/L	>10 μkat/L
Respiratory				
Acidosis: pH [39]	7.10–7.19	7.15–7.19	<7.10	<7.15
Alkalosis: pH [39]	7.50–7.60	7.50–7.60	>7.60	>7.60

All values rounded to the nearest tenth decimal place. All conversions between convention units and international system units performed using *AMA Manual of Style: A Guide for Authors and Editors 10th Edition*. http://www.amamanualofstyle.com/page/si-conversion-calculator.

Table 4

Adverse Event Table Clinical Entities

	Adverse Event	Serious Adverse Event
Gastrointestinal		
Necrotizing enterocolitis [40,41]		Bell Stage II or III
Intestinal perforation [42]		Intra-abdominal free air without preceding pneumatosis
Musculoskeletal		
Fracture	Fracture treated with immobilization	Fracture with any surgical intervention needed or known lasting sequelae
Respiratory		
Respiratory failure		Initiation of mechanical ventilation or some defined change
Pneumothorax	Present but no intervention required	Intervention required (e.g., chest tubes, sclerosis therapy and/or operative)
Apnea		Requiring initiation of mechanical ventilation
Pulmonary hypertension		Present and initiation of medical therapy to treat pulmonary hypertension (e.g., nitric oxide, milrinone, sildenafil)
Neurological		
Seizure [43]		Present and treated with anticonvulsant
Intraventricular hemorrhage [44,45]		Grade 3-4
Periventricular leukomalacia [46]		Present on imaging
Cardiology		
Hypotension [47]		Requiring pressors
ECG QTc prolongation [48]	460 – 485 ms	> 485 ms
Supraventricular tachycardia [49]	Episode resolves spontaneously or with vagal maneuvers	Requiring medical drug therapy or electroconversion to revert to sinus rhythm
Infectious disease		
Wound infection	Requiring only local intervention (e.g., topical antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Urinary tract infection		Positive urine culture treated with systemic antibiotics or antifungals
Cellulitis	Requiring only local intervention (e.g., antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Bloodstream infection		Positive blood culture requiring systemic antimicrobial

	Adverse Event	Serious Adverse Event
Meningitis		Positive cerebral spinal fluid culture requiring systemic antimicrobial
Ophthalmologic		
Conjunctivitis [50]	Requiring only local intervention (e.g., topical antimicrobial)	Requiring systemic antimicrobial therapy or surgery
Retinopathy of prematurity [45]	Any stage	Any stage requiring surgical or medical intervention
Otolaryngology		
Hearing impairment [51]		Confirmed hearing loss, either unilateral or bilateral
Drug mediated		
Infusion related reaction	Mild transient reaction or reaction that responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids)	Prolonged reaction that does not respond promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids) or life-threatening reaction that requires urgent intervention
Infusion site extravasation	Erythema with or without associated symptoms (e.g., edema, pain, induration, phlebitis)	Significant tissue injury leading to ulceration, necrosis, operative intervention indicated, or urgent intervention indicated
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching, lipodystrophia, edema)	Significant tissue injury leading to ulceration, necrosis, operative intervention indicated, or urgent intervention indicated
Allergic reaction	Transient flushing, rash, drug fever that responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics)	Prolonged reaction that does not respond promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids) or life-threatening reaction that requires urgent intervention
Anaphylaxis [52]	Acute onset of illness with skin and/or mucosal tissue manifestations and either respiratory compromise or hypotension that requires parental medication intervention	Acute onset of illness with skin and/or mucosal tissue manifestations and either respiratory compromise or hypotension that is life-threatening and requires urgent intervention