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Clinical Trials of Drugs Used Off-label in Neonates: Ethical Issues and Alternative Study Designs

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Abstract

The use of drugs for indications unapproved by the Food and Drug Administration, often called “off-label use”, is widespread in children, including neonates. The widespread off-label use of drugs in neonates presents ethical and safety challenges. Since the passage of the Best Pharmaceuticals for Children Act in 2002, both the Food and Drug Administration and National Institutes of Health have taken initiatives to facilitate and encourage research to achieve the necessary labeling for drugs routinely used in infants and children. Federal regulations provide broad rules and guidance for the protection of human subjects in research. However, there are ethical issues that a physician may face when designing clinical trials of drugs in neonates that are routinely used off-label and widely believed to be beneficial. We attempt to describe these ethical challenges and provide recommendations, including alternative study designs, to resolve them in an ethical framework that takes into account the Belmont Report, the statement of the World Medical Association, and federal regulations.

Keywords

Off-label; unlicensed; ethics; neonates; clinical trials; active control; placebo; alternative study designs; neonatal emergency research

INTRODUCTION

In the United States (US), the Food and Drug Administration (FDA) will approve a drug if it has been shown to be safe and efficacious for a particular medical condition. However, once the drug is approved based on clinical trials, usually conducted in adults, it may be used by a physician for any medical condition or any age group not listed on the labeling or in the package insert. This use of approved drugs, often called “off-label use”, is widespread in children including neonates.(American Academy of Pediatrics Committee on Drugs 1996; Blumer 1999; Avenel, Bomkratz et al. 2000; Banner 2002; O'Donnell, Stone et al. 2002; Cuzzolin, Zaccaron et al. 2003; t Jong, Eland et al. 2004)

Neonates are constantly undergoing maturation and differentiation which can alter pharmacokinetics and end-organ responses.(Kearns, Abdel-Rahman et al. 2003; Ward 2006) Therefore, clinical trials in adults or in older children cannot predict the pharmacokinetics and end-organ responses of neonates, as evidenced by numerous examples of therapeutic misadventures with off-label drug use in neonates.(Knight 1994; Blumer 1999; Griffin 2000; Ahlfors 2001; Cooper, Griffin et al. 2002; Kearns, Abdel-Rahman et al. 2003) Over the last few years, new federal laws and regulations have been instituted to address the problem of off-label drug use in children. (FDA Modernization Act of 1997–1998; FDA 1998) On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) was passed to facilitate studies of drugs used off-label in children. (United States. Congress. Senate. Committee on Health Education Labor and Pensions. 2001) Since the passage of the BPCA, the American Academy of Pediatrics, in collaboration with the National Institutes of Health (NIH) and FDA, has identified drugs commonly used off-label in children that will be required to be studied for safety. (Best Pharmaceuticals for Children Act 2003) Of the drugs that have been “short-listed” for research, six are also commonly used in neonates: dopamine, dobutamine, azithromycin, furosemide, spironolactone, and lorazepam.(Steinbrook 2002; Best Pharmaceuticals for Children Act 2003)

STATEMENT OF THE PROBLEM

The present off-label use of drugs in hundreds of thousands of children without the knowledge of efficacy and risks involved is worrisome and raises several ethical issues. (Roberts, Rodriguez et al. 2003) The situation poses an even greater risk to neonates in that the off-label use of drugs during this critical period of development also may be associated with a fetal programming effect.(Barker 2004) The question, then, arises: Should society accept randomized clinical trials (RCT) involving drugs used off-label in a finite number of neonates rather than continue the use of drugs in neonates without full knowledge of their safety, pharmacokinetics, or efficacy? If so, what additional protections for vulnerable neonates will be required and how will ethical issues be resolved?

The Belmont Report recommended special protections for research involving vulnerable subjects, including children. (World Medical Association 1979; Commission 2001) In addition according to federal regulations, some basic ethical conditions need to be satisfied for children, including neonates, before an Institutional Review Board (IRB) can approve research. (45 C.F.R 46.404; 45 C.F.R 46.405; 45 C.F.R 46.406; 45 C.F.R 46.407; 45 C.F.R. 46.205) These federal regulations are based on the degree of risk, benefit, and likelihood of yielding generalizable knowledge from the proposed research. Because the prevailing off-label use of drugs may be associated with some direct benefit to the neonates, Sections 46.405 and 46.205 in the Code of Federal Regulations (C.F.R) are most applicable for the protection of neonatal subjects (45 C.F.R 46) involved in clinical trials of drugs used off-label. The “prospect of direct benefit” as recommended by the Belmont Report is one of the key features of ethical conduct in research involving children. (World Medical Association 1979) The Belmont Report also recommends that each research intervention be evaluated for risks and benefits. This method is now called “component analysis” by the National Bioethics Advisory Commission and the Institute of Medicine and is endorsed and expanded by others.(Commission 2001; Field and Behrman 2004; Nelson 2005)

Although these special protections are in place, conducting RCTs of drugs used off-label in neonates may pose significant ethical challenges, especially when standard practice involving use of such drugs is widely believed to be beneficial despite the lack of well designed studies to support such practice.(Clark and Leaverton 1994; American Academy of Pediatrics Committee on Drugs 1995; Emanuel, Wendler et al. 2000; International Conference on Harmonisation 2001; Amdur and Biddle 2001; D’Agostino, Massaro et al.

2003; Horng and Miller 2003; Perlman 2006; Roth, Adatia et al. 2006; Short, Van Meurs et al. 2006) This paper addresses ethical issues that may be present when conducting RCTs involving drugs used off-label and offers some recommendations to resolve or reduce these ethical issues including alternative study designs.

ETHICAL ISSUES

Ethical issues may arise when designing RCTs, enrolling subjects, obtaining informed consent, and analyzing data. Each of these ethical issues is described below.

a) Ethical issues arising from the research design

A fundamental ethical premise of conducting an RCT is “equipoise”.(Freedman 1987) Freedman’s helpful concept of clinical (collective) equipoise asserts that equipoise exists if there is genuine uncertainty within the expert medical community, and not necessarily on the part of the individual investigator, with regard to the comparative therapeutic merits of the treatments being studied in a trial.(Freedman 1987) In this view, it is ethical to conduct an RCT when scientific evidence is insufficient to establish consensus among the expert medical community regarding the superiority of an intervention for a particular medical condition in a specific age group. Once the need to conduct an RCT has been established, one of the major ethical challenges for the investigators is to design a trial for neonates that will minimize risk while maximizing benefits to the subjects. A poorly designed RCT may not provide useful data and may place the subjects at risk without potential benefits. The two most commonly used research designs for conducting RCTs in neonates are:

1. Active controlled trial (ACT) using an active control with equal allocation
2. Placebo controlled trial (PCT) using a placebo with equal allocation

i) Ethical issues arising from ACTs—Although the PCT has been the ‘gold standard’ in the development of new drug therapies, the fifth revised version of the Declaration of Helsinki and others have questioned this approach if a proven treatment exists for the studied disease.(Rothman and Michels 1994; World Medical Association 2002; Berg 2005) If an effective treatment is available, some investigators avoid PCTs in an effort to minimize risk to participants. In these situations, an ACT is employed that involves a “comparator” rather than an inert placebo.

The goal of an ACT is to establish the equivalence or non-inferiority of a new treatment compared with a standard treatment (active control).(Ellenberg and Temple 2000; Temple and Ellenberg 2000; Djulbegovic and Clarke 2001) Ethical issues may arise when conducting an ACT if the evidence for the efficacy of the active control is weak to moderate. Equivalence and non-inferiority trials are based on the assumptions that the superior efficacy of the active control over placebo has been proven for a given indication and that this efficacy will be preserved under the conditions of the trial if the trial is repeated (i.e., the trial has “assay sensitivity”).(Ellenberg and Temple 2000; Temple and Ellenberg 2000) If either of these assumptions is not valid, the results may be very difficult to interpret since they rely on evidence external to the trial regarding the effect of the active control compared to a placebo.(Ellenberg and Temple 2000) Several such ACTs (e.g., doxapram as an active control versus caffeine for apnea) have been previously performed in neonates in the absence of efficacy and safety data for the active control.(Henderson-Smart and Steer 2000; Subhedar and Shaw 2003; Osborn 2005) An ACT may lead to findings suggesting that both treatments are equivalent but they may both be ineffective. Non-inferiority trials involving active comparators may perpetuate the use of therapeutic agents with small benefit-to-risk ratio, or worse, with long-term adverse consequences that cannot be detected during the course of the trial. Hence, except in life threatening situations, ACTs should only be

undertaken when the superior efficacy of the active control over the placebo has been established and “assay sensitivity” is assured.

Although an active control with prior established superior efficacy over placebo is preferred when designing an ACT, such an active control often is not available for neonatal studies that will be required for drug labeling. Lorenz and Paneth have delineated the quality and use of clinical evidence in support of a given therapy as proposed by the US Preventive Services Task Force (Table 1). (Lorenz and Paneth 2003) This grading of clinical evidence may also be useful in considering the appropriateness of using a certain drug as an active control.

If the superior efficacy of the active control over the placebo has not been demonstrated, a trial with three arms, one of which involves administration of a placebo, will allow the investigators to compare 1) the experimental agent and active control individually to the placebo and 2) the experimental agent to the active control. (Gomberg-Maitland, Frison et al. 2003) A second option is to conduct an “add-on” trial described later.

ii) Ethical issues arising from PCTs—The PCT often is selected not only because it is the most valid means of determining efficacy and safety of the drug, but because it typically requires a smaller number of subjects to detect a treatment effect than an ACT, resulting in decreased time and cost involved in conducting the study. (Berg 2005) The opponents of ACTs also believe that with the larger sample size that is required with an ACT, more adverse events are possible and, if the drug is ineffective, more participants will remain acutely ill (non-responders) compared with a PCT.

However, ethical challenges exist in conducting PCTs of drugs used off-label, as is evident from the recent newborn drug development workshop sponsored by the NIH and FDA. (Perlman 2006; Roth, Adatia et al. 2006; Short, Van Meurs et al. 2006) These ethical challenges may be resolved by considering the following guidelines based on the ethical framework for PCTs in adults as proposed by Amdur et al. (Amdur and Biddle 2001)

The first step is to determine if a placebo is going to be used in place of an existing standard therapy. A PCT is ethically justified if no standard treatment exists. If standard therapy exists, a PCT may be justified in most cases if the efficacy or safety of the standard therapy has not been established as exemplified by a recently conducted PCT to evaluate long-term safety of caffeine therapy used for apnea of prematurity. (Schmidt, Roberts et al. 2006) Because the superior efficacy and/or long-term safety of most neonatal drugs have not been established in properly designed RCTs, PCTs are ethically justified in most cases and are considered ideal for the evaluation of the efficacy or safety of drugs. However, in life threatening conditions such as neonatal hypotension, a PCT involving milrinone may not be ethically justifiable and an ACT using dopamine or dobutamine should be considered. Another option is to consider one of the alternative study designs described later to reduce the possible risk of exposure to inferior treatment.

When a standard therapy is considered to be effective in the study population, the toxicity of the standard therapy can be considered to justify the use of a PCT if the degree of toxicity of standard therapy is such that parents of neonates routinely refuse therapy (e.g., a PCT involving steroids for chronic lung disease). When standard treatment is effective and is not associated with any serious side effects, other conditions must be evaluated to determine whether or not a PCT is ethical. These conditions described in the revised Declaration of Helsinki report include the following: 1) the risk of placebo is limited to minor and temporary discomfort and proper informed consent is obtained; 2) compelling scientific

justification exists to conduct the study using a placebo; and 3) valuable knowledge can be gained and investigators have disclosed the administration of a placebo. (Ferriman 2001)

However, the most challenging ethical dilemma in conducting PCTs of drugs used off-label arises when only Grade II or III evidence (Table 1) for the efficacy of the given drug exists. In a given situation, clinical equipoise may exist but individual (theoretical) equipoise may not exist. One of the controversial aspects of the use of placebo in a given situation is the trade-off between the risks to the subjects and the potential benefit to society. The Declaration of Helsinki emphasizes that concern for the interests of the subject must come before the interests of science and society and every subject participating in the study should be assured of the best proven diagnostic and therapeutic management. (World Medical Association 1994) Of course, as some have noted, this is a condition that can never be met; after all, the new treatment may not be effective. (Temple and Ellenberg 2000) The Declaration of Helsinki statement conflicts with Freedman's concept of clinical equipoise whereby expert members of the medical community recognize that a PCT is needed to resolve an important therapeutic issue even though individual members may differ with regard to their preferences for the treatment. This concept is consistent with the idea that clinical equipoise is more important ethically than individual equipoise and a PCT may be ethically justifiable. Freedman's recommendation regarding clinical equipoise may pertain more to research in adults than to research involving a vulnerable group such as neonates. The question remains whether we should err on the side of caution when dealing with vulnerable neonates and not routinely recommend PCTs for drugs used off-label with Grade II evidence supporting their efficacy.

In circumstances such as those outlined in the revised report of the Declaration of Helsinki, specifically when safety data of these drugs used off-label in neonates are not available (i.e., compelling scientific justification exists) and the risk of placebo is limited to temporary and minor discomfort, it may be ethical to conduct PCTs involving drugs that have supporting evidence of efficacy as exemplified by the recently concluded PCT involving caffeine in premature infants. (Ferriman 2001; Schmidt, Roberts et al. 2006) For life-threatening conditions, however, where the use of placebo may be associated with harm, PCTs are ethically not justifiable and ACTs or one of the alternative study designs described later should be considered to reduce the risk of exposure to inferior treatment such as placebo.

b) Ethical issues with enrollment of subjects

An ethical dilemma may arise when physicians consider enrolling their patients in a RCT. The view of a given neonatologist on an "equipoise" issue (individual equipoise) may or may not coincide with the prevailing "clinical equipoise" of the medical community. Suppose that an ACT involving an effective treatment versus an investigational drug for a condition is being conducted (e.g., milrinone vs. the active control dobutamine for hypotension), and a neonatologist has the opinion that dobutamine is better than milrinone with respect to efficacy. (Osborn 2005) The neonatologist feels obligated to inform and advise the baby's parents regarding his or her preference for dobutamine in the baby's best medical interest. This obligation creates a barrier to the enrollment of patients in the RCT. Two strategies are often used to resolve the ethical dilemma in favor of enrolling patients in RCTs.

According to one strategy, a treatment recommendation for dobutamine is not justifiable in the absence of safety data or if the recommendation is based on Grade II to III evidence. (Ambalavanan and Whyte 2003; Lorenz and Paneth 2003) The neonatologist can explain to the parents that although he/she has a preference for dobutamine, there is a lot of disagreement in the expert medical community about this issue and it is important to subject it to formal study in order to resolve this disagreement.

According to another strategy, a neonatologist has an obligation to inform the parents of the baby of his or her treatment preference, even when the preference is based on Grade II or III evidence. Also, the neonatologist has the obligation to obtain informed consent, which will involve explaining to the parents the risks, benefits, and reasonable alternatives to the recommended treatment and offering the opportunity for her to choose an alternative treatment, if feasible. In the given situation, either administration of milrinone outside the trial or enrollment in the ACT comparing dobutamine and milrinone is a reasonable alternative to administration of dobutamine, because dobutamine is not known definitively to be superior to milrinone. (Best Pharmaceuticals for Children Act 2003; Osborn 2005) While obtaining consent, it is left to the parents to place a greater value on participation in a study that will contribute to science and to the well-being of neonates in the future rather than following the neonatologist's recommendation. Therefore, a neonatologist who follows proper informed consent procedures can both recommend a preferred treatment and ask the parents whether they are willing to enroll their baby in the RCT. A slower enrollment rate is possible in the case, where the neonatologist has a preference for the treatment. The neonatologist can enhance recruitment by informing the parents of the difference between strong and weak evidence and that his or her preference is only based on weak to moderate evidence. In addition, it can be explained that RCTs often have contradictory findings compared with those seen in published non-randomized studies, underscoring the importance of the present RCT. From the ethical perspective, the neonatologist is obligated to offer the parents the opportunity to enroll their baby in a RCT, even if they prefer a treatment based on Grade II or III evidence. Both of these strategies also apply to the resolution of ethical issues involved in enrollment of subjects in PCTs involving drugs used off-label.

c) Ethical issues with the consent process

Several neonatal drugs are used for acute clinical conditions. A different ethical issue may arise in the context of emergency neonatal research (ENR). For ENR, when an intervention must take place within a short period of time, such as the use of hypothermia for birth asphyxia, seizure medications for neonatal seizures or dopamine for hypotension, seeking consent for entry into a trial may aggravate the parents' distress. In some situations, it is not possible to obtain the consent from either parent quickly. (Morley 1997) The experience of parents involved in the consent process for an extracorporeal membrane oxygenation (ECMO) trial suggests that adequate understanding of the nature and purpose of the research is not possible with the time constraint and the stress involved in the care of sick infants. (Snowdon, Garcia et al. 1997) This situation violates the principle of autonomy that is an essential requisite for informed consent. Other studies have suggested that parents who consent for pediatric emergency research are less educated and have fewer social supports. (Harth and Thong 1995) If this also is true for ENR, neurological outcomes may not be generalizable if socio-economically disadvantaged neonates are disproportionately included in trials; thus, the research may be considered to be unethical if it does not produce sufficiently generalizable knowledge. This ethical issue related to ENR may be resolved by one of the following: 1) exception from informed consent requirements for emergency research, 2) waiver of consent and, 3) antenatal notification and/or consent. (FDA 1996; FDA 1997)

To foster emergency research for life threatening conditions, the FDA has amended the informed consent regulation by providing a narrow exception to the requirement for obtaining and documenting informed consent from each human subject. (FDA 1996; FDA 1997) Although the subject population covered in this amended rule is, in a sense, a particularly vulnerable population by having no capacity to decide about medical treatments (Shamoo 2006), the regulation does not exclude any special subject population including

neonates. In addition, the agency (FDA 21 C.F.R 50.24) has safeguards in the rule to protect special subject populations including: 1) appropriate prior animal and preclinical studies; 2) reasonable risks to subjects in relation to anticipated benefits; 3) community consultation and disclosure; 4) informed consent when feasible; 5) informing the family at the earliest opportunity; and 6) adequate data monitoring.

Although the IRB has the right to approve waiver of consent for minimal risk studies, Secretarial approval is required for emergency research that requires waiver of consent. The requirements for the Secretarial approval of waiver of consent by the Department of Health and Human Services (DHHS) are very similar to the FDA requirements for exception from informed consent. Since most of the ENR required for drug labeling is regulated by FDA, exception from informed consent according to the FDA regulations may be a better option. (FDA 1997) It appears that both FDA and DHHS have taken a utilitarian role and encouraged an increasing role for society in ethical issues pertaining to emergency research.

A modified approach for the informed consent process, specifically for ENR conducted within the first 24 hours after birth is antenatal notification or consent.(Morley 1997). This is based on the parental experience with the ECMO trial which clearly suggested that adequate understanding of the nature and purpose of the research is not possible with the time constraint and the stress involved in the care of sick infants.(Manning 2000) This undue stress and time constraint may violate the principle of autonomy. Antenatal notification may help parents prepare for participating in research and involves informing parents that the hospital is engaged in ENR to evaluate new therapies and that it is difficult to obtain consent in an emergency. If the parents are interested in additional discussion, specific research can be discussed. This approach allows enough time for the parents to read about and understand specific research and ask questions under less stressful circumstances. Antenatal notification may be followed by the informed consent process conducted during the antenatal period or after the baby is born when the circumstance arises for specific ENR. The antenatal consent process will require identifying in advance the specific neonatal population with a condition who are at extremely high risk for a serious event, e.g., neonates with hemolytic jaundice (known fetal history of Rhesus sensitization) who are at higher risk for developing kernicterus. (FDA 1996) If the consent is obtained during the antenatal period, the parents should be informed as soon as the baby is involved in the trial. In a less studied opt-out system, the parents' consent is presumed following antenatal discussion unless they had refused to participate antenatally, or after inclusion of their baby in the trial.(Manning 2000) One can argue that such a process will lessen parental distress and will be socially acceptable when conducted during less hurried and frightful circumstances than when conducted after delivery of a sick infant. The opt-out system may be kinder by allowing more than enough time to opt-out and by decreasing the burden of having to decide whether or not to consent. In order to provide fair opportunity to opt-out, the antenatal discussion should preferably be done as soon as possible once the potential subject has been identified so as to give parents ample time to evaluate the risks and benefits of participating in the research. One such possible period for antenatal discussion is when antenatal consultation with the neonatologist is requested by the obstetrician. The existing limited literature on an opt-out system involving research in children suggests that the opt-out system is socially acceptable, may be kinder, and may increase recruitment.(Rogers, Tyson et al. 1998; Manning 2000)

d) Ethical issues with data analyses

A different ethical issue may arise when trials are stopped prematurely based on interim data analyses. Currently, the ethical rationale for stopping trials early for reasons of efficacy is based on the principle that equipoise has been disturbed and physicians are obligated, therapeutically, to treat the individual patient. However, by stopping trials earlier, valuable

information may be lost about the risks of the treatment to the research subjects, as exemplified by earlier dexamethasone trials in neonates. (Halliday and Ehrenkranz 2000) Although therapeutic benefits may emerge early in the course of a trial, using drugs without knowing the risk-benefit ratio may lead to unfortunate consequences. More importantly, stopping the trial early based on efficacy may lead to the need to conduct additional trials to resolve issues of possible longer-term adverse effects, exposing even more neonates to the risks of research. Recently, a non-exploitation ethical framework for stopping RCTs was proposed to shift the weight of ethical responsibility from a provision of medical benefits to the prevention of undue harm (Table 2). (Buchanan and Miller 2005) According to this framework, the stringency of the “stopping” guidelines should be proportional to the gravity of the harm incurred by withholding an efficacious treatment. The temporary withholding of the benefits of treatment until a clinically meaningful benefit has been established with a high degree of confidence is justified by the valuable knowledge to be gained about the long-term toxicities of the investigational drug. We believe that this framework could be approved under Section 46.405 because it has the prospect of medical benefit.

ALTERNATIVE STUDY DESIGNS

An important ethical issue that may arise when conducting conventional RCTs of drugs used off-label is how to minimize the risk involved with exposure to possibly inferior treatment. One of the major challenges involved in the implementation of PCTs of drugs used off-label is acceptance by neonatologists because of a “possible exposure to inferior treatment (placebo)” when the study drug is widely believed to be beneficial. (Roth, Adatia et al. 2006; Short, Van Meurs et al. 2006) One approach to minimize the risk of exposure to inferior treatment is a fixed randomization scheme that has unequal allocation. (Palmer and Rosenberger 1999) This is similar to conventional randomization, except that instead of a 50:50 allocation, twice (or thrice (2:1 or 3:1)) as many participants are randomized to the drug arm of the study than to the placebo arm. This strategy tends to be used more for recruiting purposes, however, than for addressing the ethical issue at hand, mainly because the (fixed) allocation does not take into account evidence that is accumulating throughout the trial.

Another approach is to use a fully sequential design with equal group allocation. (Whitehead 1997; Palmer and Rosenberger 1999) In the commonly used group sequential design, the sample size is fixed in advance and data are monitored by a Data and Safety Monitoring Board after groups of subjects have completed the study to determine whether or not the trial should be modified (or halted) on the basis of safety or efficacy. However, with a fully sequential design, the sample size is not known in advance and data are monitored continuously. The accumulating results are evaluated to determine whether or not there is a significant benefit of treatment according to a pre-determined stopping boundary. The trial is planned by specifying a significance level, power, and type of stopping boundary (e.g., triangular boundary). The expected sample size can be calculated under various assumptions concerning the treatment effect. The expected sample size will be larger than that for a conventional fixed sample size trial under the assumption of no treatment effect, but it can be considerably smaller than that required for a conventional trial or one that uses group sequential monitoring if the treatment effect is large. In this case, the ethical issue is addressed by halting the trial as soon as a significant benefit of treatment is detected, leading to the exposure of fewer subjects to inferior treatment.

An alternative approach is to use a response adaptive design. There are two well-studied response-adaptive designs that are based on an urn model and are applicable to clinical trials that have two treatment arms (A and B) and binary outcomes (success or failure). A design that is well studied in neonates is the randomized “play-the-winner” rule. (Rosenberger

1999) At the beginning of the study, an urn contains X “A” balls and Y “B” balls (typically $X = Y$). On subject recruitment, a ball is drawn and replaced. If it is an “A” ball, the subject receives treatment “A”; if it is a “B” ball, the subject receives treatment “B”. A success with treatment “A” or a failure with treatment “B” will result in adding a certain number of “A” balls to the urn, while a failure with treatment “A” or a success with treatment “B” will result in adding a certain number of “B” balls to the urn. Thus, the probability of being assigned to the (currently) superior treatment is greater than 50%.

A similar adaptive design is the randomized “drop-the-loser” rule.(Coad and Ivanova 2005) At the start of the study, there are X balls for both treatments “A” and “B” in the urn, and there are Z so-called “immigration (I)” balls. The immigration balls ensure that the urn does not get emptied. When a neonate is enrolled, a ball is drawn and the subject is assigned the treatment according to the ball drawn. If the “I” ball is drawn, the ball is replaced and one additional ball of both “A” and “B” are added to the urn. If a success is observed with the “A” treatment, the “A” ball is returned to the urn; if a failure is observed with the “A” treatment, the ball is not returned to the urn. The drop-the-loser rule appears to be more promising in that there is less variable allocation and a smaller number of neonates who have treatment failures compared with the play-the-winner rule. These adaptive designs can be combined with a sequential design to further reduce the exposure to inferior treatment. (Coad and Ivanova 2005)

The adaptive designs outlined here have limitations (Palmer and Rosenberger 1999; Rosenberger 1999). They are more applicable with treatments that are not thought to be associated with significant toxicity. Adaptive designs are only suitable when the outcome is binary and there is little to moderate delay in its ascertainment. They have the potential of suffering from accrual bias whereby subjects wish to be recruited later in the trial in order to maximize their chances of receiving the superior treatment. This is only a concern in situations where subjects have the ability to decide when to enroll and when it is impossible to mask the number of subjects that have been previously entered into the trial. Time trends in subject characteristics can also be a problem in these designs because the theory that underlies the analysis of data from these designs assumes that the response probability is constant over time. Short recruitment periods are advocated to help avoid this problem. Logistical aspects such as the randomization process are challenging but are generally not too difficult to overcome. Finally, the statistical issues involved in the design, evaluation of the design’s operating characteristics, and data analysis are relatively complex and require careful attention.

If an effective standard therapy exists and there is a need to conduct a PCT for a study drug, an alternative approach is to randomize subjects to the standard therapy plus placebo or standard therapy plus the study drug. In these “add on trials” which involves the use of standard therapy in both arms of the study, there are no ethical issues pertaining to the use of placebo because placebo is used in addition to, but not in place of, standard treatment. This, of course, will be applicable only when the treatments have different mechanisms of action, and such trials do not permit conclusions concerning monotherapy.

In a situation where there is some, but inconclusive, evidence for efficacy of an investigational drug, the use of a cross-over design, in which all participants eventually receive the investigational treatment and, therefore, its possible benefit, may be ethical. (Hyman and Shore 2000) However, cross-over studies are applicable mainly for chronic, stable conditions and are best suited for short-term therapy.

CONCLUSIONS

Several ethical issues may arise when conducting RCTs of drugs used off-label in neonates, including issues related to study design, subject enrollment, informed consent, and data analysis. Active control equivalence (or non-inferiority) trials may not produce valuable information in the absence of reproducible results in prior efficacy trials of the standard therapy. PCTs with or without incorporation of alternative study designs to reduce exposure to inferior treatment may be the best approach for conducting trials, particularly for non-life threatening conditions. PCTs, when ethically acceptable, can protect society from the harm that may result from approving medical therapies based on false-positive results from active control equivalence trials. The recommendations offered here to resolve ethical issues when designing trials, enrolling subjects, obtaining informed consent, and analyzing data should be very useful to neonatologists involved in RCTs of drugs used off-label.

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Abbreviations

FDA	Food and Drug Administration
BPCA	Best Pharmaceuticals for Children Act
NIH	National Institutes of Health
RCT	randomized clinical trial
PCT	placebo controlled trial
ACT	active controlled trial
ENR	emergency neonatal research
CI	confidence interval
IRB	Institutional Review Board
US	United States
DHHS	Department of Health and Human Services
ECMO	extracorporeal membrane oxygenation
CFR	Code of Federal Regulations

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Table 1

Grading of clinical evidence as proposed by the United States Preventive Service Task Force

Level of Evidence	Quality of evidence
Grade I (Strong)	Evidence is based on at least one well designed randomized controlled clinical trial
Grade II (Moderately strong)	Evidence is based on a controlled clinical trial without randomization or cohort studies or case-control studies
Grade III (Weak)	Evidence is based on opinions of respected leaders in a given field or reports from expert committees.

Table 2

Ethical framework for stopping a randomized clinical trial based on an interim analysis

Nature of the Primary Outcome Variable	Stopping Guideline [‡]
Mortality	Treatment effect is statistically significant
Major morbidity (e.g. chronic lung disease)	Lower confidence bound for the treatment effect equals or exceeds the specified effect size the trial was designed to detect (minimal clinically meaningful effect)
Minor morbidity (e.g. time to reach full enteral feeding)	Lower confidence bound for the treatment effect exceeds a maximally acceptable value that varies inversely with the seriousness of the outcome variable

[‡]The significance level (or confidence coefficient for the confidence interval) should be appropriately adjusted for the repeated interim analyses.