**Enrollment of Neonates in More Than One Clinical Trial**

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**Abstract**

Since the highest rates of morbidity and mortality in neonates are seen in those born at <32 weeks gestation, this group has the most urgent need for novel therapies to improve survival and outcome. Legislative efforts in the US and Europe have attempted to address this issue by requiring the study of drugs, biological and nutritional products, devices, and other therapies in this population through a combination of high quality regulatory and clinical trials, quality improvement initiatives, and observational studies. Because there are relatively small numbers of very preterm neonates born each year in any one country or continent, and a significant number of clinical trials are recruiting at any one time, a neonate may meet enrollment criteria for more than one clinical trial. Neonatal units that have the infrastructure and resources to engage in research frequently face the question of whether it is permissible to enroll a neonate in more than one trial. This article examines the pertinent scientific, ethical, regulatory, and industry issues that should be taken into account when considering enrolling neonates into multiple clinical studies.

**Introduction**

Many common neonatal care practices and therapies have never been rigorously evaluated with adequate efficacy and safety data to support formal regulatory approval. As a result, most treatments have evolved into “best practice” and “standard of care” with insufficient evidence to support safety, efficacy, dosage, and treatment exposure. The compelling need to advance neonatal drug development has been recognized and has resulted in US and European legislation mandating more studies in this unique population. To develop the tools, standards, and approaches needed to accomplish this, the FDA and the Critical Path Institute with support from the pharmaceutical industry established the International Neonatal Consortium (INC) which brings together regulators, neonatologists, nurses, pharmaceutical companies, funding organizations, and parent/community groups to advance regulatory science and address the needs of neonates.(1,2) However, neonates are seen as a highly vulnerable population, with their participation in drug development and clinical trials limited by numerous factors.

Since the highest rates of morbidity and mortality are seen in neonates born <32 weeks gestational age, this group has the most urgent need for novel therapies to improve survival and outcome. Because a small fraction of live births occur at <32 weeks gestation (1.5% in the US)[3](#_ENREF_3), there are numerous clinical trials recruiting at any one time and a relatively small population of premature or ill neonates available for enrollment. A country-wide sampling of the annual number of preterm neonates born before 32 weeks gestation revealed approximately 3,500 in Canada in 2012(4), 8,300 in England and Wales in 2015(5), 7,100 in Japan in 2015(6) and 63,000 in the US in 2015(3). The expertise and resources needed to conduct these studies tend to be concentrated in a limited number of neonatal intensive care units (NICUs), where most neonates may be eligible to participate in more than one clinical trial at a time.[4](#_ENREF_4)(7) In order to continue to successfully improve neonatal survival and outcome, we must study drugs, biological and nutritional products, devices, and other therapies in parallel through a combination of high quality clinical trials, quality improvement initiatives, and non-interventional studies. With the constraints of the small population of eligible neonates, progress will be limited unless alternatives to restricting enrollment to a single clinical trial are considered, including developing new methodologies and study designs. This article examines the pertinent issues that should be considered when enrolling neonates into multiple studies.

**Scientific Considerations When Enrolling a Neonate in More than One Clinical Trial**

An initial approach is to consider the goal of clinical research--to gather reliable information about the balance between safety and efficacy for each product or intervention under investigation. Though each trial seeks to standardize research-related variables, there is the additional challenge of practice variability that occurs within and among NICUs. Although this “background noise” may preclude detection of an effect of the intervention being tested, allowing practice variations may better simulate how the intervention performs under real-world conditions. When deciding whether to allow enrollment of neonates in more than one study, the impact of practice variability on interpretation of study results should be considered.

How will enrollment of neonates into more than one trial impact the validity of each individual trial? Each trial describes clinical events with some level of accuracy, attributes clinical events to one or more products or interventions, and assigns a degree of reliability to the description and attributions. These characteristics lead to hazards that may arise in all trials which can include: 1) detection errors - the trial may fail to describe an event because the event is too rare, the event is not detected due to investigator error, or there is a failure in data collection; 2) misattribution - the trial may falsely attribute an event to the intervention or may fail to attribute an event to the trial; and 3) uncertainty - the information may not be precise enough for its intended use.

The extent to which these hazards may occur is variable and can lead to consequences of misattribution or uncertainty such as: 1) reducing the precision of estimates of safety or efficacy, including altered effect size if the interventions have opposite effects or if the interventions are synergistic; 2) misattributing events that could contribute to assessments of safety or efficacy to one intervention or another (trial or non-trial related); and 3) alterations in drug disposition – related to enzyme induction or drug effects (for example, competitive antagonism at a receptor that is the intended or an unintended target) that will depend on the temporal relationship between administration of the interventions. During early phase trials, proximate consequences could include imprecision in pharmacokinetics (PK) or PK/pharmacodynamics (PD) relationships.

 Drug-drug interactions (DDIs) are a major concern for concurrent studies. Pharmacologic (e.g. medications for pain) or non-pharmacologic interventions (e.g. kangaroo care for pain) may ameliorate or exaggerate the true effect of each intervention. The following types of interactions are determinants of the intensity, quality or duration of drug response: 1) PK interactions where one drug inhibits or accelerates metabolism and elimination of the other, 2) PD interactions where drugs may act at the receptor or effector level masking the true effect of the interventions, or 3) simple chemical incompatibilities which would negate the effects of the drugs being given together. The need to perform requisite evaluations of drugs for neonates must address this conundrum with respect to drug interactions.

 Early phase clinical trials require definition of true pharmacologic effects on safety and potential efficacy in a small number of neonates. Simultaneous co-enrollment should be avoided to generate accurate PK data and evaluate PD with minimal interactions, to allow proper design of advanced protocols. In randomized trials, studying two or more drugs or non-pharmacologic interventions with known interactions of any type should be avoided. Convenience sampling from neonates who receive multiple medications for clinical indications with known interactions (e.g. drugs for patent ductus arteriosus closure and aminoglycosides) may be useful.

**Strategies to Consider When Planning for Co-enrollment**

While enrollment in more than one clinical trial can be highly problematic, there are other instances where it may be permissible (**Table 1**). For example, enrollment into more than one simultaneous or sequential clinical trial should be avoided if the primary endpoints of the two trials are similar, as attribution of main effects to one or the other trial would be extremely difficult. The exception would be if the trials were combined in a factorial design, where participants are randomized to one or more interventions from the outset (i.e. 4 arms including standard of care, intervention A, intervention B, and interventions A+B). The impact of each arm’s treatment on the primary endpoint can then be evaluated. However, factorial trials require a substantial increase in the sample size to evaluate interactions between interventions. (8–10)

Enrollment into more than one trial also should generally be avoided when each of the trials are evaluating a novel therapy, since the disposition of the new drugs may not be well characterized and robust safety or efficacy information may not be available. Drugs that are not approved or marketed for a neonatal indication, but have been widely studied and are considered current standards of care, may not be subject to this restriction if other criteria are met for safety evaluation and scientific integrity.

There are several scenarios where enrollment into more than one trial is unlikely to compromise safety or scientific validity of either trial. Short PK and/or safety studies or device validation studies separated by a scientifically-determined period of time from an interventional study may be permissible. In Myles’ review of ethical and scientific considerations for concurrent enrollment, co-enrollment may be permitted if the following three conditions are met: the likelihood of enrollment into study B has not been influenced by treatment in study A; if neither treatment influences the natural course of disease of the other condition being studied; and if there is unlikely to be a drug-drug interaction. (9) The review highlights consideration of the potential increased burden of various study procedures as well as sample size adjustments and potential selection biases.

If co-enrollment is considered, it will require exploration of scientific details including: 1) the temporal relationship between the antecedents of the effects (whether the causal pathways of the relevant events overlap in time); 2) what is known about the treatment(s); 3) the phase of development for each product; 4) the temporal relationships between interventions in each trial; 5) whether there are overlapping absorption, distribution, metabolism, and excretion (ADME) pathways; 6) whether there are potentially overlapping toxicities; and 7) whether enrollment in an additional study may be treated as a covariate in the statistical analysis.

Comparative effectiveness trials, in which two or more accepted strategies or treatments are being evaluated, may utilize the covariate strategy to enable co-enrollment. Since the potential for co-enrollment is high in neonatal studies, it should be considered during protocol development. Absolute decisions about co-enrollment should be avoided and specific language addressing when co-enrollment may or may not be permissible should be included in protocols. Specific limitations should be based on informed, well-reasoned judgment or statistical criteria. Other strategies that may be considered when planning neonatal studies in which the question of co-enrollment may arise include: 1) accepting a low level of co-enrollment when it is thought to be unlikely to lead to serious consequences and may facilitate recruitment; 2) adopting a conservative approach with no co-enrollment allowed, which may lead to difficulty finding an adequate number of study sites, increased competition among studies, and ultimately slow research progress; and 3) clinical trial simulation and modelling to generate quantitative estimates of the range and magnitude of the risks and/or interactions.

In summary, the scientific validity of a clinical trial may be undermined by co-enrollment through a potential effect on the statistical power of the individual trials and/or an interaction between the two interventions. (7,9) An interaction may also lead to different conclusions about safety and/or efficacy of one or both interventions that might not have been apparent in separate clinical trials.(9,10) In addition to concerns about statistical power, increased risk of adverse events (AE) and the interpretation of study results, there may be a problem with outcome ascertainment bias. (11) Thus, whether or not to allow co-enrollment in more than one clinical trial requires a careful assessment of the potential impact on the study results, interactions between the interventions, subject safety and the scientific validity of the clinical trials. (12–15)

**Ethical Considerations When Enrolling a Neonate in More than One Clinical Trial**

The primary principle to consider as stated by the International Conference on Harmonisation in its Guideline for Good Clinical Practice (ICH-E6), is that the child’s interest should always prevail over that of science and society. This is paramount when assessing and monitoring risks. There are several ethical issues that must be addressed if co-enrollment in more than one clinical trial is to be allowed: 1) co-enrollment may inadvertently increase the risks and burdens beyond those that would otherwise have been allowable for each clinical trial considered alone, especially for non-beneficial (e.g. “research only”) procedures such as blood draws; 2) the impact of either allowing or disallowing co-enrollment in more than one clinical trial on parental decision-making must be considered; and 3) co-enrollment must not undermine the scientific validity of either clinical trial.

Parental Permission: Not allowing parents to co-enroll their neonates in studies that they would want to support and whose risks and benefits have been explained to them appears to restrict their right to exercise such choices on behalf of their neonate.(9) While it may be reasonable to restrict co-enrollment if it would undermine the scientific validity of the clinical trials, this does not address the question of which clinical trial should be offered to the parent(s). Allowing co-enrollment, when scientifically appropriate, respects the role of parents in deciding for their neonate and may result in a more representative population of those neonates who would receive the two interventions in clinical practice. (7,9,11) There are no data to indicate that it may be too stressful and thus unethical to approach parents about co-enrollment in multiple studies. (10) One study demonstrated that most mothers of neonates were willing to participate in more than one study. (7) In another study, most parents (74%) of preterm neonates were comfortable with enrollment in more than one study at any one time with a minority (22%) being worried about the number of studies. (16) Co-enrollment did not appear to have an impact on recruitment. (13) When co-enrollment is an appropriate option (whether at the same time or in sequence), parents should be fully informed about the available studies including any potential interactions between the studies (for example, the chances of an unknown drug-drug interaction). Although it appears that parents are generally supportive of co-enrollment, it is important to recognize that having a critically ill neonate can be difficult and parents should be supported throughout the entire clinical trials process. (16,17,18)

Risks and Burdens of Participation: According to FDA regulations, a non-beneficial (or "research only") procedure must present no more than minimal risk (21 CFR 50.51) or no more than a minor increase over minimal risk (21 CFR 50.53). Outside of the US, existing regulations and/or guidance limit such procedures to no more than minimal risk, yet neither define minimal risk nor define it as comparable to the routine clinical experience of the enrolled research population. (19) This is the approach taken by the addendum to the ICH E-11 to harmonize the US with other approaches. Within the US, minimal risk is usually limited to routine physical and psychological examinations of healthy children. The category of minor increase over minimal risk is not defined, but is limited to children with the disorder or condition (suggesting that this level of risk is similar to the routine clinical care of children enrolled in the research, consistent with international guidance on minimal risk). Perhaps for this reason, ICH E-6 uses the term "low risk" to describe the appropriate risk level for non-beneficial procedures performed on individuals who are unable to consent for themselves. An individual procedure may qualify as either minimal risk or a minor increase over minimal risk, but when performed multiple times over a limited period of time, the overall risk may exceed an acceptable threshold. Thus, co-enrollment may result in a risk exposure that exceeds minimal risk/minor increase over minimal risk. As such, a research ethics committee should be aware of the possibility of co-enrollment and approve this possibility in advance.

Observational studies may not involve a change in clinical treatment but additional blood draws and/or monitoring could place an additional burden on a neonate. While that burden for an individual study may be reasonable, the additive effects of multiple studies may be unreasonable. (7) Blood sampling for both clinical care and research must be coordinated to minimize discomfort and to keep the total volume of blood drawn within acceptable limits. (15)

**Regulatory Considerations When Enrolling a Neonate in More than One Clinical Trial**

Regulatory agencies and the International Council for Harmonization (ICH) have not issued comprehensive guidance regarding co-enrollment. Adherence to the principles of sound trial design and scientific validity is critical in the assessment of whether co-enrollment may be considered. Regulatory agencies, with their charge to protect the public health, must thoroughly consider the potential safety implications of any study design alongside its potential to demonstrate efficacy.

While Health Canada (HC) does not have any regulations specific to Pediatrics in general or neonates in particular, the conduct of clinical trials in children from birth to 18 years of age can be requested as necessary. HC does have Guidelines that allow for flexibility in regulatory decision-making, as long as a suitable scientific and clinical rationale is provided. This could potentially allow enrollment of neonates into more than one trial when deemed scientifically and ethically sound. Consideration should be given to the duration and timing of each study together with its measured outcome(s) as well as the potential to utilize non-standard or adaptive designs and analyses.

A Paediatric Investigation Plan (PIP) and/or waiver covering the entire pediatric population, including neonates, is mandatory for the authorization of a new medicinal product in the European Union. These are reviewed and agreed by the Paediatric Committee at the EMA in the framework of the Paediatric Regulation (Regulation (EC) No 1901/2006). In addition, EMA can provide advice on clinical trial protocols through its Scientific Advice Working Party. Whereas co-enrollment is not specifically referred to and the considerations outlined in this paper with respect to scientific, safety and ethical considerations are valid, there are opportunities to discuss such approaches at EMA through scientific advice(20) or during the PIP procedure.(21) The authorization of clinical trials occurs at each Member State level. (22)

Enrollment of neonates in more than one regulated clinical trial or one regulated trial and a non-FDA regulated trial has been permitted by FDA in specific circumstances. FDA Draft Guidance, “Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors,” issued in 2014, references participation in more than one clinical trial. The Draft Guidance states, “FDA strongly discourages these practices as enrollment in more than one clinical investigation could increase risks to subjects, particularly because they may be exposed to more than one investigational product for which the safety profile may not be well understood. Undoubtedly, enrollment of a single patient in studies of two or more novel agents would increase risk and potentially confound safety and efficacy assessments.”

Many neonatal therapies have been utilized off-label for decades or longer. For those drugs, the safety profile may be reasonably well known. Clinical trials employing standard therapies may be acceptable alongside a novel treatment trial as long as principles of scientific validity are met (separate target organ systems and/or primary endpoints). Regulatory agencies are also invested in the principles of parental permission and consent, and co-enrollment may be accompanied by specific considerations in the permission process. Although regulatory agencies may differ in approach to co-enrollment for neonatal trials, the fundamental concerns are consistent – retaining the scientific and statistical validity of individual studies, maintaining the ability to detect significant AEs, ensuring parental permission is both informed and voluntary, and importantly, allowing access to investigational agents when there are no approved treatments for a given condition.

**Industry Considerations When Enrolling Neonates in More than One Clinical Trial**

Drug developers within pharmaceutical companies are keenly aware of the challenges of recruiting and performing neonatal clinical trials, especially with extremely preterm neonates. Enrollment can be exceedingly slow, even when performing trials to prevent Bronchopulmonary Dysplasia (BPD), one of the most common diseases affecting preterm neonates. An analysis of recruitment rates in large studies evaluating BPD prevention (as either a primary or secondary endpoint) was recently performed by Chiesi Farmaceutici. A total of 11 completed studies were identified and the average enrollment duration was nearly 4 years, with one trial lasting over 7 years. The average recruitment rate was 1.3 neonates/site/month, with a range of 0.4 – 4 (Table 2).

These prolonged periods of enrollment have resulted in few drugs being adequately tested in neonates. Therefore, industry investigators support the concept of allowing participation in more than one study at a time for neonates: 1) who are cared for at sites with appropriate expertise, 2) who have parents willing to have their neonate participate in research, and 3) who meet entry criteria. However, co-enrollment must be carefully evaluated with the support of scientific review and regulatory guidance, to determine under which conditions this would be permissible.

First, one must assess the type of studies to be considered for co-enrollment. For example, studies of a preventative therapy for BPD at the same time as a preventative therapy for retinopathy of prematurity (ROP) would be difficult to analyze, as these morbidities are believed to have common etiologies. However, a neonate who participated in an early prevention trial may later be considered for eligibility in a treatment trial for established complications of extreme prematurity.

Although many observational trials could be performed within the same time frame as the investigational drug trial, the drug may have an impact on the results of the observational study. Non-pharmacologic studies (nutritional agents) may be viewed to have small effects on drug study outcomes. However, poor growth during the neonatal period can impact neonatal morbidities as well as later neurodevelopmental outcomes. Thus, the challenge of studying a new investigational drug and discerning which AE or serious adverse events (SAE) can be ascribed to the new drug is challenging. Comprehensive safety and AE data is not available for the majority of neonatal therapies and therefore evaluating AE with more than one investigational drug can be difficult. If the event is serious, the uncertainty of the potential causative agent could place a promising compound at risk, not only for neonatal use but for even for older age groups.

Due to these concerns, many pharmaceutical companies have adopted a policy in which neonates may not be enrolled in a new trial until at least 30 days after the end of active participation in a prior trial. Operationally, there also are complications if the two studies are performed using agents developed by separate companies where different standard operating procedures may exist and proprietary concerns pose challenges to data sharing. Trial procedures such as monitoring policies, consent processes, case report forms, data entry, and AE reporting may further complicate the studies and make them more prone to errors. Under the right scientific and operational circumstances, concomitant studies should be considered, but only with very careful consideration of the proposed concomitant trials.

**Conclusions**

Provided the scientific, ethical and safety aspects of co-enrollment can be adequately addressed, there should be no barrier to the co-enrollment of eligible neonates in more than one clinical trial. Careful consideration of the risks and benefits both to the neonate and to the research studies must occur prior to any co-enrollment. While participation in more than one clinical trial using similar therapeutic targets and/or primary outcome measures should be discouraged, studies involving different conditions that involve a different therapeutic target organ and different primary outcome measures may be permitted following agreements between the investigators, sponsors, and other regulatory bodies. The regulatory agencies consider adequate safety monitoring, scientific rigor and validity, and informed, voluntary parental consent to be paramount. In addition to facilitating more rapid enrollment into much-needed neonatal clinical trials, co-enrollment may allow for access to investigational agents for conditions without approved therapies.

**Table 1: Co-enrollment in Clinical Trials**

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| --- | --- |
| **Avoid Co-enrollment** | **Co-enrollment May be Permissible** |
| Early phase PK studies | Brief PK and or safety/studies |
| Randomized trials studying two or more drugs or interventions with known interactions | Device validation studies |
| Trials with similar primary endpoints | Factorial study designs with adequate sample sizes |
| If each trial is specifically targeting the same organ system | Trials of drugs routinely used and considered standard of care for neonates |

**Table 2: BPD Prevention Trials: Sites, Recruitment and Target Population (Source: Chiesi Farmaceutici)**



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