



Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Potential confounders and risk factors for adverse events in neonatal trials: Points to consider

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Description	This tool gives examples of potential confounders and risk factors for adverse events/ outcome in neonatal trials
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Adverse event, Outcome, Confounder, Risk factor

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Disclaimer: Sponsors and researchers unfamiliar with clinical trials in neonates and/or neonatology are advised to seek expert advice due the complexity of neonatology.

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Introduction

Safety data of individual or pooled clinical trials are analysed using descriptive statistics.¹ The data analysis of neonatal studies takes the variability of the neonatal population and its continuous changes into account.²⁻⁴ At the time of planning a neonatal trial it is helpful to remember that safety data analyses do consist of a planned part, based on the population specific safety profile of the study drug, and review of any new safety signals.⁵⁻⁷ The planned data analysis is usually described in the safety analysis plan (SAP), which is part of the protocol. New safety concerns may emerge during the trial or after data lock. These may originate directly from the neonatal trial or may emerge from the literature. Any new safety signal will need careful evaluation of the relevant evidence, including a consideration of any missing data.⁵⁻⁷

Potential confounders and risk factors for adverse events/ outcome in neonatal trials

Safety data collection and analyses are based on the population specific safety profile of the study drug.^{1,2,8} This includes identified and potential risks as well as any missing information in the study population.⁸ Differences in the type and frequency of adverse drug reactions (ADRs) and possible difference in the clinical presentation of ADRs compared to older children and adults are considered at the time of planning data collection for a neonatal trial.^{1,2,6,8}

The statistical analysis of neonatal safety data of considers issues such as confounders and risk factors for adverse events/ outcome, sample size, ever changing reference values (e.g. laboratory data, vital signs), frequent off-label use of comedication, growth and development and overall outcome.^{2, 9-12} [Table 1](#) lists examples of potential confounders and risk factors for adverse events/ outcome in neonatal trials which might be considered at the time of planning the safety data analysis.¹³⁻¹⁹

The outcome assessment in neonatal trials is a composite endpoint of the treatments received and their combined benefit-risk. It includes an overall assessment of the neonate such as weight, length, head circumference and neurodevelopmental status.^{2,20} Since the presentation of some ADRs or safety outcomes such as neurodevelopmental delay may only become apparent after a lag time, repeated analyses of outcome might be needed.² The definition of drug specific safety outcomes will depend on its neonatal safety profile.

One of the challenges in neonatal research is that diagnosis and treatment of the disease of interest as well as relevant comorbidities, which may modify treatment related outcomes, may vary between different neonatal intensive care units (NICUs) and/or physicians.²¹⁻²⁶ Since most neonatal trials are multicentre and often multi-country studies these differences should

be considered at the time of trial conception. This may, for example, include an observational study of the incidence of the disease to be studied including standards for diagnostic procedures and criteria, treatment, follow up and outcome.^{24,25,27}

Conclusions

Safety data analyses of neonatal trial data require a thorough understanding of the safety profile of the study drug in the general and neonatal population at the time of writing the protocol, as well as expertise in neonatology and drug safety. Data analysis takes into account the considerable variability of the neonatal population which may include risk factors or confounders for ADRs. Therefore, it is recommended to seek support from an experienced pharmacovigilance physician, ideally with neonatal experience.

Competing interests

All authors consider not having any competing interests for this tool. BA has worked for GlaxoSmithKline between October 2006 and September 2009 and holds company shares. Between October 2009 and May 2015 she has worked for Novartis.

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Table 1. Examples of potential confounders and risk factors for adverse events/ outcome in neonatal trials

Examples of data items to be considered		Examples of references
Parents	Potential toxins (e.g. alcohol, smoking, recreational drugs, environmental toxins)	1, 2
	Socio-economic status	3
Pregnancy	Medical history of mother prior to and during pregnancy	1,4
	Medication history of mother prior to and during pregnancy (including over-the-counter medications)	1,5
	Medication history of father	6
	Singleton or multiple pregnancy	7
Delivery	Duration of rupture of membranes	1
	Drugs administered during delivery	1
	Mode of delivery (spontaneous, instrumental, elective or emergency caesarean section)	1
	Signs/evidence of infection	8
Neonate at birth	Gestational age at birth (consider including in methods section how this was assessed)	9
	Birth weight	10
	Birth weight for age and sex (percentile or z-score, small or large for gestational age)	1
	APGAR scores	11
	Sex	12
Neonatal period	Comedications: including start and stop dates, dose, frequency, duration and dose modifications (incl. intravascular fluids, parenteral nutrition and transfusions)	13,14
	Excipients: daily and total exposure to excipients from all medications	15
	Medication errors (e.g. type of errors with date and time)	16
	Differences in treatment protocols in multi-centre trials	17
	Comorbidities and how these are diagnosed and treated (e.g. intraventricular haemorrhage, jaundice, infections)	14
	Procedures (e.g. vascular access, intubation, surgery)	18
	Feeding (e.g. type of nutrition, initiation of feeding)	19, 20,21
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