Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Safety data analyses of neonatal trials: Points to consider

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Description	This tool provides practical points to consider when planning for the analysis of neonatal safety data
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Safety data analysis

Authors: Beate Aurich, Valéry Elie,
Naura Mahmoudi, Evelyne Jacqz-Aigrain

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

Correspondence email: pedcrin@ecrin.org

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Introduction

Safety data of individual or pooled clinical trials are analysed using descriptive statistics. The data analysis of neonatal studies takes the variability of the neonatal population and its continuous changes into account. 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. 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.

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Safety data collection and analyses are based on the population specific safety profile of the study drug.[1,2,3] This includes identified and potential risks as well as any missing information in the study population.[3] 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.[1,2,3,4]

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, 5-6] Table 1 provides a checklist of points to consider when designing a Safety Analysis Plan for a neonatal trial. Where appropriate prenatal confounders or risk factors are included in the analyses.[7-8] (see Table 2)

Sample size

One of the challenges in neonatal research is sample size. Willhelm et al. noted that the most common reason for inconclusive Cochrane reviews of neonatal studies was the relatively small number of neonates included in trials.[9] This does not only impact the conclusion on efficacy, but also limits the robustness of the conclusions for drug safety. Not all safety issues can be predicted and risk factors such as prematurity and confounders (e.g. comedication) may need to be taken into account requiring data stratification thus further reducing statistical power.[10,11] The frequency of an adverse drug reaction (ADR) determines how likely it is to occur in a given study population. For example, a common adverse drug reaction with a frequency of 1% may or may not be observed in a study with 50 neonates.[12]

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Reference values for laboratory data and vital signs

In the neonatal period many reference values for laboratory data and vital signs change with gestational age and/or postnatal age. These changes are organ and function specific and occur progressively at different points in time throughout the neonatal period and beyond.[13,14] Safety data analysis of neonatal trials takes these changes into account.

Off-label use of comedications

Off-label and unlicensed prescription of medicines is common in the paediatric population and neonates are at highest risk.[15,16] Off-label and unlicensed use is associated with an increased risk of ADRs and medication errors.[15-17] The safety data analysis of neonatal clinical trial data takes these confounding factors into account in addition to the standard consideration of potential interactions.[18]

Growth

The measurement of growth includes weight, head circumference and length.[19] It is not only expressed in the respective continuous variables (i.e. centimetres, gram) but also as percentile or z-score for gestational age in premature neonates and chronological (post-natal) age in term neonates.[20,21]

Due to the considerable variability in the neonatal population in terms of gestational age and weight, mean/median values are of limited value. Growth data is most commonly analysed and presented by standardised gestational age group because prematurity is a risk factor for adverse outcome.[2,14,22,23] The use of population specific growth charts should be considered at the time of protocol writing.

Insufficient weight gain in neonates is an overall indicator for disease.[19] Therefore it is good practice to examine data for clinically significant changes in growth.[2,19]

Safety outcome

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.[2,23] 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.[24-25] 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

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study of the incidence of the disease to be studied including standards for diagnostic procedures and criteria, treatment, follow up and outcome.[26,27,28]

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. Safety data analysis of neonatal trials: Check list of points to consider

Points to consider in safety data analyses	Considered	Not considered	Not applicable	Comments/notes
Age appropriate reference values for laboratory data				
Haematology[1]				
Biochemistry[2,3]				
Age appropriate reference values for vital signs				
Heart rate[4]				
Blood pressure[5]				
Respiratory rate[6]				
Population specific reference values for growth				
Premature neonates[7]				
Trisomy 21[8]				
Healthy neonate born at term[9-11]				
Population specific reference values for neurodevelopment				
Bayley scale[12,13]				
Population specific safety outcome				
Neonatal safety profile of study drug (identified and potential risks, missing information)[14-18]				
Confounders and risk factors[16,19-21]				

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