Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Neonatal trials and data analysis by age group: Points to consider

V 1.0, 22 March 2021

Description	This tool proposes a check list for the analysis of age-related data in neonatal trials
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Age groups, Data analysis

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

Inserm

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

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

Introduction

In neonatal clinical trials age reflects changes in pharmacokinetics and pharmacodynamics and factors modifying efficacy and safety. For example a neonate born at 24 weeks gestation does not have the same metabolic capacities as one born at 39 weeks. Similarly, developmental maturation and with it, reference values for laboratory parameters and vital signs change rapidly in neonates. Data collection and analysis needs to take all these factors into account.

Neonatal trials and data analysis: Points to consider

Age should be analysed and reported by age category and mean/median. Age is not rounded up in neonates. Care should be taken to ensure that postmenstrual and corrected age in premature neonates is correctly calculated over time. Existing age group standards should be used where possible.[1,2,3]

The description of the characteristics of the study population should include at least gestation age (GA) at birth and chronological (postnatal) age and postmenstrual and/or corrected age by standard age group at the start of study drug treatment. Similarly, postmenstrual age and/or corrected age should be included at the time of assessment of study objectives (e.g. pharmacokinetic sampling). Data analysis by age group facilitates adjustment for maturation, changing reference values and risk factors for morbidity and mortality (Table 1). It is therefore important to consider how at the time of writing the protocol how organ maturation correlates with standard neonatal age group strata and how this impacts study endpoints.[4] Consideration should be given to plan anaylses based on standard age categories in order to facilitate meta-analyses and to add study specific analyses as required. Including neonates from various age group strata may need a careful assessment of how differences in confounders and risk factors for outcome may influence study endpoints.

Conclusions

In conclusion, in neonatal clinical trials age is a proxy for maturity and of covariates influencing morbidity and mortality. It is therefore important to stratify data analysis by age groups and include in the protocol how gestational age is determined. Existing standard age categories should be used to facilitate comparison with published data and future meta-analyses. However, additional age groups may be considered based on the study population and trial objectives.

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

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.

References

1. Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016 Jul;215(1):103.e1-103.e14. doi: 10.1016/j.ajog.2016.01.004.
2. World Health Organisation (WHO), International Federation of Gynecology and Obstetrics (FIGO). WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977;56(3):247-53. Available at : https://doi.org/10.3109/0001634 7709162009
3. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World Health Organization. Geneva, 2012. Available at: https://www.who.int/pmnch/media/news/2012/201204 _borntoosoon-report.pdf
4. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67.

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046

Table 1. Defining the target population – Data analysis in neonatal trials: Check list*

Data items	Described in the analysis plan	
Gestational age at birth by age category		
	Yes	
	No	
	Not applicable	
Mean/median gestational age		
At birth	Yes	
	No	
	Not applicable	
At start of study drug treatment	Yes	
	No	
	Not applicable	
At completion of study drug treatment	Yes	
	No	
	Not applicable	
At pharmacokinetic sampling	Yes	
	No	
	Not applicable	
At end of follow-up	Yes	
	No	
	Not applicable	
At discharge/transfer from hospital	Yes	
	No	
	Not applicable	
Postmenstrual and/or corrected age by age category		
At start of study drug treatment	Yes	
	No	
	Not applicable	
At completion of study drug treatment	Yes	
	No	
	Not applicable	
At pharmacokinetic sampling	Yes	
	No	
	Not applicable	
At end of follow-up	Yes	
	No	
	Not applicable	
At discharge/transfer from hospital	Yes	
	No	
	Not applicable	

* Not exhaustive

PedCRIN has received funding from the European Union's Horizon 2020 programmer under grant agreement number 731046