Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Exclusion criteria in neonatal trial protocols: Points to consider

V 1.0, 22 March 2021

Description	This tool illustrates in a worked example how existing safety data from the product label/ summary of product characteristics can inform exclusion criteria of a neonatal protocol
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Drug safety, Exclusion criteria

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

Inserm

<u>Disclaimer:</u> 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

During protocol development the safety profile of a drug is considered in multiple sections such as the objectives, exclusion criteria, reporting of serious adverse events, safety data collection and follow-up.[1] One way of reflecting on inclusion and exclusion criteria and the question of patient safety during protocol development is to study the Summary of Product Characteristics (SPC) of the study drug and the SPCs of drugs in the same class or similar products.[2] In addition, inclusion and exclusion criteria are also based on potential confounding factors and need to be consistent with Good Clinical Practice (GCP).[1]

Exclusion criteria and patient safety

Patient safety in neonatal trials takes the heterogeneity and variability of the population into account. This includes for example gestational age, chronological age, weight, comorbidities and comedications.[3-5] Data analysis of neonatal trials can be challenging due to the considerable number and variability of possible confounding and risk factors which can influence drug response[3,5] Narrow inclusion criteria may reduce the number of these factors, but may slow attrition rates and provide less information on the benefit-risk profile of the drug in routine clinical care.[6]

Risk factors and confounders for adverse events and adverse drug reactions (ADRs) inform the selection of exclusion criteria in neonatal clinical trials. Risk management of ADRs may lead to the exclusion of subjects with known risk factors for ADRs (Table 1). Exclusion criteria will, for example, consider disease severity, gestational age, comorbidities, comedications and abnormal laboratory and vital signs.[1,4] Exclusion criteria take the maturational changes of neonatal reference values for laboratory values and vital signs into consideration, which occur progressively at different points in time throughout the neonatal period and beyond.[3,5] Table 1 provides a hypothetical example of how existing information in the SPC can be used to write protocol sections on inclusion and exclusion criteria with a particular focus on drug safety related issues.

Other exclusion criteria (e.g. the signature of the informed consent by parents/ legal representative) will need to be considered for a neonatal protocol. They depend, for example, on the characteristics of the target population (e.g. gestational age group, birth weight), trial objectives (e.g. efficacy, pharmacokinetics, safety), confounding factors for outcome (e.g. death due to major congenital malformations) and practical issues (e.g. long-term follow up).

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

Conclusions

Drug safety plays an important role throughout the protocol development process in a variety of protocol sections. A thorough understanding of the safety profile of the study drug in the general and neonatal population at the time of writing the protocol is important. In addition expertise in neonatology and pharmacovigilance are necessary to ensure inclusion and exclusion criteria are adapted to the neonatal population. Therefore it is recommended to include an experienced pharmacovigilance physician, ideally with neonatal experience, in the protocol review process.

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. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). ICH Harmonised Tripartite Guideline – Guideline for Good Clinical Practice E6(R1). Current Step 4 version10 June 1996, Geneva. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/ E6/E6_R1_Guideline.pdf
2. European Commission (EC). A guideline on summary of product characteristics (SmPC), Note to applicants, Revision 2, September 2009. Available at: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
3. 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.
4. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). ICH Tripartite Guidelines - Clinical investigation of medicinal products in the pediatric population E11, Current Step 4version, 20 July 2000, Geneva. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/ guidelines/Efficacy/E11/Step4/E11_Guidelines.pdf
5. 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.
6. Food and Drug Administration (FDA). Public workshop – Evaluating inclusion and exclusion criteria in clinical trials – Workshop report. The National Press Club, Washington, DC, 16 April 2018. Available at: https://www.fda.gov/ downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDARA/UCM613054.pdf

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

Table 1. Exclusion criteria and patient safety: Examples of how information of the Summary of Product Characteristics can support the development of exclusion criteria for a neonatal trial protocol (not exhaustive)

Criterion	SPC sections which may provide guidance	SPC of Drug A‡	Example wording for neonatal protocol for Drug A
Exclusion criteria	4.3 Contraindications	Hypersensitivity to the active substance of Drug A or to any of the excipients listed in section 6.1	- Hypersensitivity or known intolerance to Drug A or any of its excipients - Sepsis with an organism known to be resistant to Drug A
	4.4 Warnings and precautions	Drug A may cause renal impairment and should be used with care in patients requiring haemofiltration or peritoneal dialysis	- Renal failure requiring haemofiltration or peritoneal dialysis
	4.5 Interaction with other medicinal products and other forms of interaction	Concomitant administration of other nephrotoxic drugs may increase the nephrotoxicity of Drug A	- Concomitant treatment with other nephrotoxic drugs
	6.1 List of excipients	Drug A contains alcohol as an excipient	- Concomitant treatment with drugs containing propylene glycol as an excipient[1]

SPC= Summary of Product Characteristics

† Other inclusion and exclusion criteria (e.g. the signature of the informed consent by parents/ legal representative) need to be added into a neonatal protocol and depend for example on the characteristics of the target population (e.g. age group, birth weight), trial objectives (e.g. efficacy, pharmacokinetics, safety), confounding factors for outcome (e.g. major congenital malformations) and practical issues (e.g. long-term follow up).

‡ The SPC of "Drug A" is invented to provide an example of how existing information in the SPC can be used to write protocol sections on inclusion and exclusion criteria with a particular focus on drug safety related issues.

1. **Food and Drug Administration (FDA).** FDA Drug Safety Communication: Serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-serious-health-problems-seen-premature-babies-given-kaletra

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