Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Formulations used in neonatal trials: Points to consider

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Description	This tool includes a check list of points to consider for neonatal formulations
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Formulation

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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

Medicines prescribed to neonates need to have a favourable benefit-risk balance including a formulation adapted to the neonatal population which, for example, limits the risk of medication errors and does not contain excipients which are known to be harmful. Neonatal formulation development is challenging due to rapid maturational changes which may influence pharmacokinetics (PK) and/ or pharmacodynamics (PD), a heterogeneous patient population, common polypharmacy; as well as limits on fluid volume, flow rate of administration, excipients considered to be safe and route of administration. An additional challenge is that the formulation may need to be manipulated to suit neonatal dosing requirements, which may increase the risk of medication errors, lack of efficacy and toxicity.

Points to consider for neonatal formulation development

Doses for neonates are usually calculated based on weight which varies widely between patients and changes continuously. Therefore the formulation of a neonatal drug needs to be able to be administered for example to a premature neonate weighing just 500 gram and a term neonate weighing 4,000 gram. In addition, technical issues such as limitations of infusion pumps and syringes, compatibility issues of comedications administered through the same vascular access and limited vascular access need to be taken into consideration.[1,2-3] An additional challenge is that the formulation needs to be sufficiently stable under the very specific environmental conditions of neonatal intensive care units (NICUs).[4] Polypharmacy is common in neonates admitted to NICUs and over 90% of medicines prescribed to neonates are off-label or unlicensed.[1,5] Off-label and unlicensed use is associated with the need to manipulate the formulation for example by crushing tablets or dilution.[5] Medication errors due to drug manipulation and drug administration errors are common in neonates and can have serious consequences.[6] Finally, insufficient data on the pharmacokinetics of off-label/unlicensed comedications and their excipients expose neonates to the risk of lack of efficacy and toxicity.[1,3,,5] Examples of points to consider in the development of neonatal formulations are listed in Table 1. For more detailed information on the challenges of neonatal formulation developments readers may want to consider reading the article by O'Brien et al.[1]

Conclusions

Medicines used for treating neonates should have an age appropriate formulation to ensure safe prescription, preparation and administration and only include excipients which are tolerated by neonates. Researchers are advised to seek expert advice if a medicine needs to be adapted for the neonatal population in order to ensure best practice is used for its preparation and that an effective and safe dose is administered.

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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. Check list of points to consider for neonatal formulations (not exhaustive)[1]

Topic	Considered in the protocol	Not considered	Not applicable	Comments/ notes
General				
Risk of prescription error (e.g. calculation of dose)[1,2]				
Risk of preparation error (e.g. is a dilution necessary)[1,2]				
Risk of administration error (e.g. wrong route of administration; wrong infusion rate)[1,2]				
Excipients				
Formulation without excipients is available[3]				
The same excipients are used in other neonatal drugs/ formulations and are considered safe (check literature and relevant databases)[4,5]				
Infusions				
Risk of hypervolaemia (in particular in the smallest neonates and those requiring multiple medications and/or those with fluid restrictions)[1,6]				
Risk of electrolyte imbalance[1,6]				
Risk of dilution error (consider having the medication prepared in pharmacy during normal working hours)[1,2]				
Doses, including smallest doses, can be measured easily and accurately using standard syringes (calculate different doses and see if they can be drawn up; consider field testing with nurses)[1,7]				
Potential interactions with co-administered medications via the same vascular access have been studied (check the SPC of the study drug and commonly co-administered drugs, this information is usually described in section 4.4 Special warnings and precautions for use and/or 4.5 Interaction with other medicinal products and other forms of interaction)[1]				
Smallest dose can be administered using a standard pump (calculate smallest dose and see if this can be infused using a standard pump; consider field testing with nurses)[7]				
Lag-volume effects of vascular access lines has been addressed[7,8]				

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Topic	Considered in the protocol	Not considered	Not applicable	Comments/ notes
Potential interactions with the material of medical devices used for administration have been addressed (check the SPC of the study drug, this information is usually described in section 4.4 Special warnings and precautions for use)[1]				
Potential stability issues have been addressed[1]				
Topical/ transdermal preparations				
Transdermal preparations: patch size adapted or adaptable to extremely premature neonates (immature skin of premature neonates may lead to higher systemic exposure)[7]				
Topical preparations: risk of absorption, in particular in premature neonates, has been excluded[9]				
Oral formulations				
Risk of hypervolaemia (in particular in the smallest neonates and those requiring multiple medications and/or those with fluid restrictions)[1,6]				
Risk of electrolyte imbalance[1,6]				
Risk of dilution error (consider having the medication prepared in pharmacy during normal working hours)[1,2]				
Doses, including small doses, can be measured easily and accurately using standard syringes (calculate different doses and see if they can be drawn up; consider field testing with nurses)[1,7]				
Potential interactions with the material of medical devices used for administration have been addressed (check the SPC of the study drug, this information is usually described in section 4.4 Warnings and precautions)[1]				
Potential stability issues have been addressed[1]				
Risk of interaction with milk (check the SPC of the study drug, this might be included in section 4.5 Interaction with other medicinal products and other forms of interaction)[10,11]				
Risk of blocking gastric tube[12]				
Effect of neonatal gastric pH on absorption has been considered[1]				
Osmolarity is adapted to neonatal population[1]				

SPC= Summary of Product Characteristics (=Product information/ label)

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[1] For more detailed information on the challenges of neonatal formulation development readers may want to consider reading the article by O'Brien et al. Making Medicines Baby Size: The Challenges in Bridging the Formulation Gap in Neonatal Medicine. Int J Mol Sci. 2019 May 31;20(11). pii: E2688. doi: 10.3390/ijms20112688.

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