Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Outcome in neonatal trials and data collection and analysis: Points to consider

V 1.0, 22 March 2021

Description	This tool provides examples of data which may inform the planning of data collection and analysis of neonatal outcome
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Outcome data collection, Outcome data analysis

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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.**

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

Introduction

Clinical trial outcome is defined as a patient's response to an intervention, for example treatment with an antibiotic.[1,2] It can be assessed in a variety of ways including pharmacokinetics, pharmacodynamics, efficacy and safety using clinical and/or biological parameters.[1,3] It is recorded for all patients independent of treatment allocation (active and control arm) and can be subjective or objective.[1] Outcome can be assessed by health care providers, patients and observers (i.e. parents) using standardised, validated methods.[1,4] Outcome may vary between different neonatal diseases and also between neonatal intensive care units (NICU).[5] Efficacy and safety outcomes influence the evaluation of the benefit-risk ratio of treatment.[6-8] Research into neonatal outcome is currently conducted by a variety of initiatives including for example Core Outcomes in Neonates (COIN).[9]

Factors influencing neonatal outcome

Risk factors for severe adverse neonatal outcome (SANO) include for example prematurity (below 37 weeks of completed gestation) and abnormal birth weight (below 2500 gram or above 4000 gram), and can have different underlying aetiologies.[10-16] Other risk factors include congenital disease, in-utero exposure to maternal disease and medications as well as complications during delivery.[11,12,17,18]

Maternal factors and complications during delivery

Maternal diseases and complications during pregnancy and delivery can be risk factors for SANO.[19] During protocol development for multicentre trials consideration might be given to potential differences in the type and frequency of diseases in women of child bearing potential in different populations.[12,13]

Prematurity

Common conditions in preterm neonates (<37 weeks gestation) include for example sepsis, respiratory distress, intraventricular haemorrhage, hyperbilirubinaemia, persistent ductus arteriosus and necrotizing enterocolitis.[15,16,20] Whilst premature delivery is considered to be a multi-factorial process, infections are thought to be a frequent cause of premature birth and may cause neonatal sepsis and mortality.[21-23] Neonates born prematurely may have more than one risk factor for morbidity and mortality. For example, a premature neonate born at 24 weeks gestation will have a birth weight below 2500 gram and may have, in addition, a congenital malformation. During protocol development consideration should be given to how gestational age is assessed and this should be included in the methods section of the protocol.[24]

Birth weight

Both premature and term neonates may have a low birth weight.[25] Birth weight is routinely assessed correcting for gestational age and sex (percentile or z-score).[26,27] Neonates with a birth weight below the 10th percentile (z-score below -2 standard deviations) for gestational

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age are considered small for gestational age (SGA).[26] Maternal hypertension, diabetes mellitus, chronic maternal infections and congenital diseases are for example associated with SGA.[27] These SGA neonates have a higher risk of morbidity and mortality including for example necrotizing enterocolitis, severe intraventricular haemorrhage, bronchopulmonary dysplasia, polycythaemia, hypoglycaemia, hyperbilirubinaemia and severe retinopathy of prematurity.[28-30] Whilst low birth weight is associated with prematurity, it is an additional independent risk factor for adverse neonatal outcome.[25]

Diabetes, excessive weight gain in pregnancy and a maternal body mass index above 25 are associated with a birth weight above 4000 gram and large for gestational age (LGA) babies (i.e. above the 90th percentile for gestational age; z-score above +2 standard deviations).[26,31] LGA can also be associated with certain congenital syndromes.[26] LGA babies are at increased risk of birth injuries, respiratory distress, hyperbilirubinaemia, hypoglycaemia and polycythaemia.[19,27]

Comorbidities

Examples of common morbidities observed in Neonatal Intensive Care Units (NICU) include infections, gastrointestinal, cardiac, intracranial and pulmonary diseases.[32,33] Their aetiology is often multifactorial and they present clinically in a variety of ways. For example, symptoms of sepsis may include hyperbilirubinaemia, necrotizing enterocolitis, coagulopathy, hypoglycaemia and/or respiratory failure.[28,34-36] Abnormal coagulation in turn increases the risk of intraventricular haemorrhage.[37]

Comedications

The type and number of concomitant medicines are determined by the comorbidities, which in turn are influenced by the above mentioned risk factors for neonatal disease.[16,29] In addition, drug-drug interactions and drug-disease interactions should be considered because they may influence outcome.[38,39] The frequency of off-label/unlicensed use of medicines and medication errors as well as issues with the provision of age adapted formulations in NICU should be taken into account.[40-42] Off-label and unlicensed use of medicines is associated with a higher risk of adverse drug reactions and medication errors.[43,44] Additional factors, which may modify outcome, include for example possible differences between different NICUs in treatment protocols for comorbidities (i.e. criteria for initiating treatment, the specific drugs used, doses, frequency and duration of therapy).[45,46] It is important to address these potential differences at the time of protocol writing and trial set up in order to reduce bias and confounding.

Neonatal outcome: Which data should be collected?

At the time of protocol writing it might be useful to separate efficacy, safety and overall outcome assessment. These can be assessed at short-term and where applicable over the long-term. (Figure 1)

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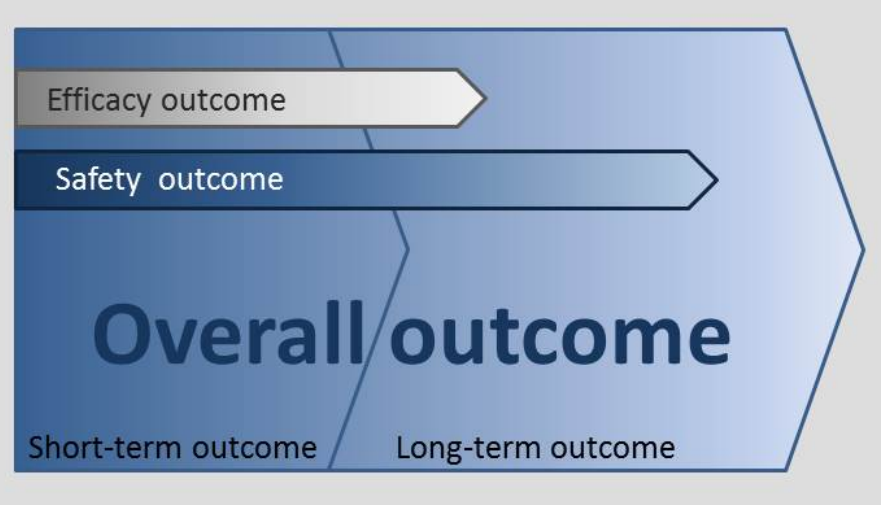

Figure 1. Types of clinical trial outcomes

Efficacy outcome

Since most neonatal trials will be multicentre studies, endpoints and biomarkers for assessing efficacy may need to be harmonised. In addition potential confounding factors and biases for efficacy related outcomes, such as comedications, should be considered and if and how these may vary between trial sites. Efficacy endpoints used in other patient populations should be adapted to neonates (Table 1).[47]

Safety outcome

Safety endpoints in neonatal trials should be adapted to the study population. They are based on the understanding of the safety profile of the study drug, i.e. identified and potential risks and missing information in neonates.[48] (EMA 2018) Standard safety outcomes in neonates include for example growth and neurodevelopment (Table 1).[49]

Overall outcome

The overall outcome of neonates is the result of all treatments and interventions, including those received in the context of a clinical trial and routine clinical care. Initiatives such as COIN are currently developing overall neonatal outcome criteria.[50] (COIN 2018) Examples of data items which may inform the analysis of neonatal outcome are provided in Table 1.

Conclusions

Assessing outcome in neonates is complex. Key factors influencing neonatal outcome include, for example, maternal disease, in-utero drug exposure, birth weight, gestational age at birth, comorbidities and comedications. Therefore, analysis of clinical trial data needs to be stratified by risk factors and confounders for outcome. The methods of neonatal outcome

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assessment, including the duration of follow up, for both efficacy and safety, need careful consideration as they may differ considerably from older children and adults.

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. Neonatal outcomes: Examples which may inform data collection and analysis

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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