Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Neonatal trials and standard age groups: Points to consider

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Description	This tool summarises the definitions of commonly used terms for neonatal age-groups
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Age groups

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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

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.

Defining the target population: Standardising neonatal age groups

To enable accurate calculation of the various ways of describing neonatal age, the date of the first day of the last menstrual period (LMP) or expected date of delivery calculated based on foetal ultrasound, date of birth, and current date of all observations/interventions need to be recorded in the trial database.[1] This will enable the calculation of gestational age at birth (GA), chronological age, post-menstrual age (PMA) and chronological age. Where ever possible standard age groups should be used. However, additional analyses should be considered depending on the study population and the objectives of the trial. Age is never rounded up in neonates (i.e. a neonate born at 24 weeks and 5 days gestation is a 24 week neonate).[2] The neonatal period includes the first 27 days after birth (i.e. below 28 days of life) and thus includes both term and preterm neonates.[3,4] Table 1 provides a summary of commonly used definitions.

Gestational age at birth

GA at birth is defined as the duration of gestation.[4] It is determined based on the available information at the time of delivery such as LMP, foetal ultrasound and clinical assessment at birth.[2] Depending on the duration of pregnancy neonates are born either prematurely, at term or post-term.[4]

GA at birth is expressed in completed weeks and days (e.g. 28 weeks and 3 days), and is usually estimated.[5] The original WHO standard categories for gestational age have been revised reflecting the medical progress in the treatment of premature infants. [4,5] The protocol should clearly describe how GA is determined (e.g. how it was estimated or if for example, because the different methods can change study results.[6,7] GA groups combined with birth weight reflect morbidity and mortality risks.[2,5,8,9]

Chronological (postnatal) age

Chronological (postnatal) age is defined as the time since birth (e.g. hours, days, weeks, months or years) and is applied regardless of the GA at birth.[2,10,11]

The early neonatal period is defined as 0 to 7 completed days of life which is followed by the late neonatal period (below 28 days of life).[10,11] Occasional misunderstandings arise in the way neonatal age is counted in the first 24 hours of life.[11] Therefore clinical trials during the early

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neonatal period need to ensure that the trial protocol is sufficiently clear, for example by using hours of life rather than days. This is particularly important for PK studies where rapid developmental changes may influence PK (e.g. renal function).[3]

Postmenstrual age

PMA expresses age as a function of LMP, adding up GA and chronological (postnatal) age. For example a neonate born after 27 weeks and 3 days gestation and a chronological age of 12 weeks and 6 days has a postmenstrual age of 40 weeks and 2 days.[2]

Corrected age

Corrected age is used for premature neonates under the age of 3 years.[2] It adjusts the chronological (postnatal) age for the prematurity to allow an age appropriate assessment of, for example, weight or neuro-motor development.[8]

It is measured in weeks and months and takes the expected date of delivery (=40 weeks) into account:

- Prior to the expected date of delivery it is calculated by adding gestational age to chronological (postnatal) age. For example a neonate born after 31 weeks and 3 days gestation with a chronological age of 4 weeks and 6 days has a corrected age of 36 weeks and 2 days.[2]

- After the expected date of delivery the weeks of prematurity are subtracted from the chronological (postnatal) age. For example an infant with a chronological (postnatal) age of 50 weeks who was born at 25 weeks (40 – 25 weeks = 15 weeks premature) has a corrected age of 35 weeks (50 – 15 weeks).[2]

Conclusions

In conclusion, in neonatal clinical trials age is a proxy for maturity and of covariates influencing morbidity and mortality. 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.

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. Defining the target population: Standardising age groups – Summary of definitions*

Item	Definition
Neonatal ages	
Date of birth	Day/month/year
Gestational age[1,2] (GA)	(Date of birth) – (Date of first day of last menstrual period) Expressed in weeks+days
Chronological (postnatal) age[3]	Number of days, weeks, months or years since birth
Post-menstrual age[3] (PMA)	(Current date) – first day of last menstrual period or (Gestational age) + (Chronological age)
Corrected age[3]	Used for premature neonates Prior to the expected date of delivery: ➢ (Gestational age)+(Chronological [postnatal] age) After the expected date of delivery: ➢ (Chronological [postnatal] age) – (Weeks of prematurity [= 40 - GA])
Classification of neonatal age groups	
Preterm[1,4]	Below 37 weeks (259 days) weeks GA: ➢ Moderate to late preterm: 32 to less than 37 weeks GA ➢ Very preterm: Between 28 to less than 32 weeks GA ➢ Extremely preterm: Below 28 weeks GA
Term[1]	Between 37 to less than 42 weeks GA
Post-term[1]	42 or more weeks GA
Neonatal period[1,2]	
	Below 28 days of life (i.e. includes both term and preterm neonates)
Additional classification of neonates according to weight	
Independent of gestational age[5]	
Low birth weight (LBW)	Less than 2500g
Very low birth weight (VLBW)	Less than 1500g
Extremely low birth weight (ELBW)	Less than 1000g
As a function of gestational age and sex[6-8]	
Small for gestational age (SGA)	Below the 10th percentile or Below -2 Standard deviations (z-score)
Appropriate for gestational age (AGA)	Between the 10th and the 90th percentile or Between -2 and +2 Standard deviations (z-score)
Large for gestational age (LGA)	Above the 90th percentile or Above +2 Standard deviations (z-score)

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