Conduct of clinical trials in paediatric age groups according to ICH E11
Considerations on study design, scientific, ethical and practical issues from two pediatricians
Agenda

• Introduction ICH E11
• Overview of pediatric age groups according to ICH E11
• Value and caveats of these age groups
• General principles for pediatric trials
• Preterm neonates
• Term neonates
• Infants and toddlers
• Children 2-11 years
• Adolescents
• Recurring issues in all age groups
• Conclusions
ICH E11

• “Clinical Investigation of Medicinal Products in the Paediatric Population”

• **Objective of ICH E11**
  – Encourage and facilitate timely pediatric medicinal product development internationally

• **Scope of ICH E11**
  – Considerations when initiating a pediatric program
  – Timing of initiation of pediatric studies during drug development
  – Types of studies needed (PK, PD, safety, efficacy)
  – Ethics of pediatric clinical investigation
  – Age categories
Pediatric age groups according to ICH E11

- Preterm newborn infants
  - 0 to 27 days
- Term newborn infants
  - 28 days to 23 months
- Infants & toddlers
  - 2 to 11 years
- Children
  - 12 to 16-18 years
Value of these age groups

- Attempt to provide convenient groupings
- Assist in study design
- Enrollment of older age groups first into trials
- Physiological changes
  - First 2 years of life: body composition, renal and liver function, growth, CNS maturation
  - Later: growth, CNS maturation, sex hormones
- Pediatric Investigation Plan (PIP), Pediatric Study Plan (PSP)
Caveats of using age groups

- Disease specific for a certain age group
- Disease may present differently in different age groups
- Age groups can include a large range of maturation levels - but more age groups would increase the number of total patients needed
- Different formulations may be required for different age groupings
- Endpoints could be different in different age group
General principles for pediatric trials (1)

- **Risk-benefit assessment**
  - Is there a potential benefit for the child?
  - Minimal risk

- **Selection of age groups**
  - Information should be gained in the least vulnerable population

- **Assent**
  - If and when applicable
General principles for pediatric trials (2)

• **Appropriate training and experience in clinical trials**
  - Everybody involved in these trials

• **Minimize number of patients**

• **Minimize distress**

• **Establishment of independent data monitoring committee (DMC/ DSMB)**

• **Use of placebo**
  - Only if there is no established therapy available
Preterm Neonates
Preterm neonates

Scientific/ study design considerations

- Unique disease states and susceptibility
- Neonatology is a rapidly changing field – need for expert input
- Differences in standard of care – networks may be helpful
- Device studies – lots of devices in NICU...
- Weight and age (gestational and postnatal) stratification
- Science vs practicalities – e.g. PK studies, blood volume
Preterm neonates

Scientific/ study design considerations (2)

- **Comparator and blinding** – placebo, off-label, standard of care?
- **Sick patients** – how to recognize ADR/AE/SAE?
- **Difficulties in assessing outcomes**
- **Long-term outcome measures important** – e.g. developmental FU to e.g. 6 years
- **Rarely possible to extrapolate PK data from other populations**
Preterm neonates

Ethical considerations

• Appropriateness of clinical trial in very sick babies vs need for research - clinical care vs research

• Consent from parents – emergency situation – ask pre-delivery?

• Competing studies – more than one research study available

• Off license prescribing vs clinical trials
Preterm neonates

Practical considerations

• Blood sampling – volumes/ frequency, access (IV)

• Urine sampling

• Formulation – may be nil by mouth

• Assessments to be done bedside – e.g. MRI scans may not be feasible

• PK - Drug assays on minimal amounts of blood
Term Neonates
Term neonates

Scientific considerations

• Volumes of distribution of medicinal products may be different

• Blood-brain barrier still not fully mature

• Oral dosing less predictable

• Dose adjusting over the first weeks of life - hepatic and renal immaturity
Term neonates

Ethical considerations

- Otherwise healthy infants unless disease/condition affects subject

- Consent issues
  - Mother may be sick
  - Parents divorced/not married/father not available
  - Underage mother
Term neonates
Practical considerations

• **Recruitment** - e.g. vaccine studies

• **Urine sampling**

• **Blood sampling**
  – No indwelling lines
  – May be no routine sampling

• **Formulations**

• **Feeds/sleep times**
Infants and Toddlers
Infants and Toddlers

Scientific/ study design considerations

• Rapid developmental/ physiological changes

• Pharmacokinetic challenges – need for tailored study design

• Individualization of doses between individuals but also within an individual over time

• Child friendly formulations - taste, exact dosing

• Design of outcome measures/ endpoints - e.g. nausea/ vomiting
Infants and Toddlers

Ethical considerations

- Consent from parents

- Blood sampling can be difficult in this age group
  - Limit number of samples but also number of attempts (to be defined in advance)
  - Expertise required

- “Keeping still” for procedures
Infants and Toddlers

Practical considerations

- Study activities coordinated with clinical activities
- Plan well in advance, good information to parents
- Try to plan study and clinical activities after the child’s routines
- Offer food/ place for the whole family
- Don’t forget siblings
- Use of topical anesthetics should be standard
- Urine sampling
- Use of other techniques to distract the child when performing procedures (toys, music)
Children
2-11 years
Children 2-11 years

Scientific/ study design considerations

- **Wide age group** – huge variation in growth and developmental status
- Puberty might have started in girls
- **Most pathways of drug clearance are mature** - clearance can exceed adult values
- PK in 2-4 years old least predictable
- Extrapolation might be possible in older children
- **Design of endpoints** – different endpoints within this group?
Children 2-11 years

Ethical considerations

• Assent
  – Required in older children – from school-age?, no specific age/ no legal status
  – What if dissent?

• Information process will take longer - children have to be informed according to their developmental age
Children 2-11 years

Practical considerations

• Swallowing tablets is an issue up to and beyond school age
  – Different formulation, syrup, tablet size
• Taste issues
• Visits to be fitted round school time/ siblings
• “Keeping still” for investigations
  – LP, MRI scans...
  – Sedation might be needed
• Use of distraction/ meditation techniques
  – “Day dreams”
• Preparation of the child (and the parents) is key
  – Minimize distress
Adolescents
Adolescents

Scientific/ study design considerations

• Onset of puberty – gender differences

• Conditions can be affected by hormonal changes around puberty – migraine, seizures...

• Choice of outcome measures/ endpoints – relevant to the patients, can be different to those of carers

• PK data can be extrapolated - > 12 years of age similar pharmacokinetics to adults
Adolescents

Ethical considerations

- Assent/consent/emancipated adults
- Could be parents themselves!
- Pregnancy testing
- Contraceptives
- Illegal drug intake
Adolescents
Practical considerations

• Can vote with their feet/ ask questions/ may not agree with their parents!

• Noncompliance

• Exam time – important to minimize visits and fit them around school

• Adolescents detest needles!
Solutions to recurring issues across all age groups \(^{(1)}\)

- **Blood sampling (frequency, volumes etc.)**
  - Sparse sampling for PK studies
  - Blood spots
  - Prioritization
  - Experienced phlebotomists

- **Relevant endpoints**
  - Talk to advocacy/patient groups
  - Talk to young people!
Solutions to recurring issues across all age groups \(^{(2)}\)

- **Visit scheduling**
  - Flexibility and compromise

- **Consideration of the whole family**
  - Family friendly facilities, e.g. parent/family accommodation
  - Play therapists

- **Genetic testing in minors** – storing of samples, withdrawal of consent
Conclusions
Conclusions

Although the ICH E11 age groups are arbitrary – they do help with looking at the different issues for different age groups.
Conclusions

Only guidance - may be a good reason to use different categories?
Conclusions

A specific disease may be relevant in all or just some of these categories.
Conclusions

Regulators expect consideration of all categories and a good reason if clinical studies are to exclude one or more groups in order to get a waiver from a PIP or PSP.
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