Rational age classification for inclusion of developmental subgroups in paediatric studies – Introduction

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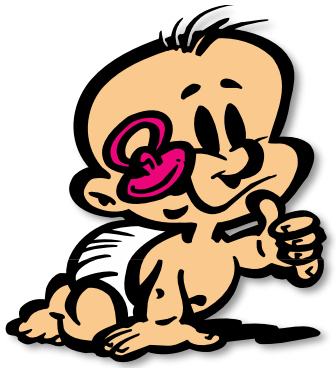

What I intend to discuss

- Regulatory view
- Developmental view (physiology, pharmacology)
- Therapeutic needs of children

No conflicts of interests to declare

European Medicines Agency

January 2001
CPMP/ICH/2711/99

ICH Topic E 11
Clinical Investigation of Medicinal Products in the Paediatric Population

Step 5

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION
(CPMP/ICH/2711/99)

TRANSMISSION TO CPMP	October 1999
RELEASE FOR CONSULTATION	October 1999
DEADLINE FOR COMMENTS	April 2000
FINAL APPROVAL BY CPMP	July 2000
DATE FOR COMING INTO OPERATION	January 2001

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH E 11(2000) Section 2.5

Any classification of the paediatric population into age categories is to some extent arbitrary, but a classification such as the one below provides a basis for thinking about study design in paediatric patients…

ICH E 11(2000) Section 2.5…

The following is one possible categorization.

- preterm newborn infants
- term newborn infants (0 to 27 days)
- infants and toddlers (28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 16-18 years (dependent on region))

Letter from Sumner Yaffe - PedFarm

Viesti

Letter from Sumner Yaffe

Spielberg, Marsha

Lähetetty: torstai 17. heinäkuuta 1997 klo 22.49

Vastaanottaja: Hoppu Kalle

Dear Kalle:

Please excuse the delay in replying to your e-mail of June 26. I have tried to find out the background for the regulations concerning age limitations in pediatric labeling of drugs. I have checked with our own IRB and also with Sandy Cohen in Detroit. Sandy thinks that some of the older labeling information stated that the drug was not to be used in children under 12 years of age. I do not know the rationale for this statement nor can I see any reason for it at the present time. At the National Institutes of Health, when children are involved in research, we obtain assent or affirmative agreement from the child who is older than 7 years of age. We require parental consent up to the age of 18 unless they are emancipated (living away from home, having had a baby, or other events of emancipation). I hope this information will be helpful to you. Please call on me again if you have any further questions.

Best regards, Sumner J. Yaffe, M.D.

ICH E 11(2000) Section 2.5….

…There is, however, considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories.

…Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant…

…Dividing the paediatric population into many age groups might needlessly increase the number of patients required.

ICH E11 (2018) guideline addendum (R1)

- General principles outlined in ICH E11 (2000) Section 2.5 continue to apply.
- Further, the arbitrary division of paediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study.
- Depending on factors such as the condition, the treatment, and the study design, *it may be justifiable to include paediatric subpopulations in adult studies or adult subpopulations in paediatric studies.*

Developmental view

- Physiological growth and biological development continue until maturation is reached
- The rate/velocity of growth and development vary within and among individuals
- Pharmacological variables do not have a simple (linear) relationship with age or size

View based on therapeutic needs of children

- Diseases unique to children
- Diseases, occurring in both adults and paediatric patients
  - In children may be similar or different from adults

- Therapeutic needs of particular concern:
  - Medicinal products needed to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options

ICH E 11 Section 2.3 – Timing of studies

2.3.2 Medicinal products intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options

The presence of a serious or life-threatening disease for which the product represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of paediatric studies. In this case, medicinal product development should begin early in the paediatric population, following assessment of initial safety data and reasonable evidence of potential benefit.

ICH E 11 Section 2.3 – Timing of studies

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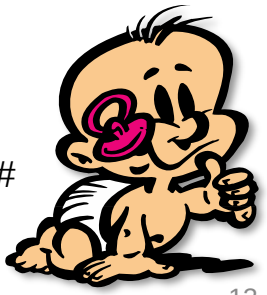
The recent Ebola virus outbreaks – West Africa 2014-2016

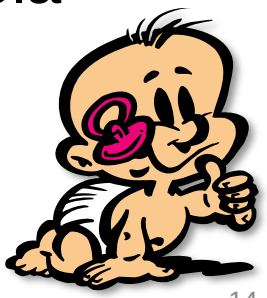
- Children played a pivotal role in the spread of the 2014-2016 outbreak centred in Guinea, Liberia, and Sierra Leone (28 610 Cases; 11 308 Deaths; 40 % Case fatality rate (CFR))
  - A 2-year old child was the first recorded case of the outbreak in Guinea (1), and a girl of similar age was the first case of Ebola in Mali (2).
- The mortality in children, particularly in those <5 yrs of age, was higher than in adults but lower than in elderly, and experience from other diseases suggest that both numbers and severity of a disease in children tend to be underestimated in RLS (e.g. TB; ref 3).

1. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. a. N Engl J Med. 2014 Oct 9;371(15):1418–25.
2. World Health Organization; [cited 2014 Oct 28] Available from: http://www.who.int/mediacentre/news/ebola/24-october-2014/en/#
3. Cruz AT, Starke JR. What's in a number? Accurate estimates of childhood tuberculosis. The Lancet Global Health. 2014



The recent Ebola virus outbreaks – DRC 2018-2019

- Current outbreak in eastern Democratic Republic of the Congo (DRC)
- As of 1 Oct, 3 197 cases; of which 2 136 died (overall CFR 67%).
- 906 (28%) children <18yrs [15% of all <5 yrs CFR 77%; 6% <1 yr (28 May data)]
- In the ongoing 2018-2019 Ebola outbreak in DRC, the first-ever multi-drug randomized control trial is being conducted to evaluate the effectiveness and safety of drugs used in the treatment of Ebola patients.
- The rVSV-ZEBOV vaccine, which proved highly protective against EVD in a major trial in Guinea in 2015, is being used in the ongoing 2018-2019 Ebola outbreak in DRC. Initial data indicates that the vaccine is highly effective.



WHO https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease [cited 2019 Oct 6]

Children and investigational vaccines and medicines for EVD

- In the West African outbreak, no children in the real CTs (?)
- In Congo (North Kivu) outbreak the protocol approved by the National Regulatory Authorities and the Ethics Committee of the Democratic Republic of the Congo considered the inclusion of children of above one year old for the ring vaccination (with rVSV-ZEBOV). [1]
- Some newspaper/websites have indicated that a few children have been treated with some investigational medicine in Congo, but it is not clear with which and whether it has been compassionate use or if they have received it in a clinical trial.

1. WHO; Ebola Vaccine FAQ https://www.who.int/emergencies/diseases/ebola/frequently-asked-questions/ebola-vaccine [cited 2019 Oct 6]

Conclusions

- Children have the right to good quality health care – the best health care possible (UN Convention on the Rights of the Child).
- In a serious or life-threatening disease for which a new product represents a potentially important advance in therapy there is a need for relatively urgent and early initiation of paediatric studies (ICH E 11).
- Serious consideration should be given to initiate the evaluation of potential paediatric endpoints as part of the adult development program prior to their incorporation into the paediatric program, and to include paediatric subpopulations in adult studies (ICH E 11 R1).
- In a Public Health Emergency of International Concern (PHEIC) caused by communicable disease, if children are not included in CTs to develop effective treatments and vaccines it will be more difficult to contain the outbreaks – and the children may not receive the best care possible.