BfArM
Federal Institute for Drugs and Medical Devices

Methodological issues in paediatric trial design

Norbert Benda – Federal Institute for Drugs and Medical Devices, Bonn

Disclaimer:
Views expressed in this presentation are the author's personal views and not necessarily the views of BfArM

Statistical limitations in pediatric trials

- Sample size
  - small
- Treatment control
  - Placebo may be impossible / unethical
- Healthy volunteers
  - not possible
- Endpoints
  - Possibly different from adults and between age groups

Statistical principles in drug approval

- Independent confirmatory conclusion
  - no use of historical data
  - type-1 error control limiting false positive approvals
- Internal validity, causality
  - Blinded randomized comparison to placebo
- External validity
  - Relevant population to study

Pediatric dilemma

- Independent confirmation
  - vs historical information
- Population concerned
  - vs extrapolation from other population
- Placebo control
  - vs active comparator possibly w/o proven assay sensitivity

Similar issues in other applications

- Strong medical need
  - False negatives could be more important than false positives
- Orphan drugs
  - sample size limited
- Ethical concerns re placebo
  - active comparator studies
- Dose adjustment
  - PK/PD modelling

Possible strategies (overview)

- Meta-analytic approaches using historical data
  - Bayesian: Evidence synthesis
- PK/PD modelling
- Non-inferiority trials (NI)
- Withdrawal design
- Adaptive designs
- Add-on designs, allow for rescue
- Surrogate endpoints (PD) + adult evidence
- Pediatric subgroup analyses

Weakened requirements to discuss

- No independent confirmation
  - proper selection possible ?
  - rely on extrapolation
  - rely on model assumption (also: in imputation in all respects)
- Type-1 error: False positives vs false negatives
- Rely on surrogate endpoints/PD
- NI: Assay sensitivity from external evidence
- External validity: design not corresponding to real life / labelling

Evidence Synthesis (Bayesian)

Use historical information on adults to define a prior belief

Pros:

- Reduced sample size
- Makes use of all relevant information on clinical endpoint

Cons:

- Rely on extrapolation
- may ignore or underestimate systematic differences between population
- Prior assumption of between trial variability critical

Violated principle:

- Independent confirmation

PK/PD modelling

Use clinical and PK/PD data in adults, PK (PD) in children

Pros:

- No clinical data /no placebo in children needed
- Makes use of PK/PD relationship

Cons:

- Rely on PK-PD-clinical relationship in adult
- Rely on extensive model assumptions
- Quantification of uncertainty may be difficult in model selection

Violated principle:

- Independent confirmation

Non-inferiority (NI) trials w/o placebo

Comparison to active comparator

Pros:

- No placebo needed
- Assessment of additional benefit compared to existing drugs

Cons:

- NI margin difficult to define in children
- Sample size high for reasonable NI margins
- Relevant comparator may not exist
- Assay sensitivity cannot be assessed / rely on external information
- Constancy of comparator effect may be difficult to verify

Violated principle:

- No proper assessment compared to placebo

Surrogate endpoints

Use surrogate endpoints in children

Pros:

- "true" endpoint may not be measurable in children
- Surrogate may be less invasive
- Trial may be shorter

Cons:

- Rely on external (adult) information (historical meta-analysis) for surrogate endpoint validation: Extrapolation of adult relationship
- Uncertainty on "true" clinical endpoint difficult to quantify: Extensive information needed

Violated principle:

- No clinical endpoint relevant for the patient

Withdrawal design

Placebo control in responders to the experimental drug

Pros:

- Placebo period shorter
- Relatively easy to conduct

Cons:

- Patients not treatment naïve
- Placebo control only in responders:
  - No comparative risk-benefit assessment in full population
  - Overestimated effect sizes possible due to real withdrawal effects
  - Underestimated effect sizes also possible leading to high sample sizes

Violated principle:

- External validity may be questioned

Add-on design

A+B vs A+Placebo with established treatment A

Pros:

- All patients are treated
- Relatively easy to conduct

Cons:

- Only possible if there is a treatment on which you can add
- Only ethical if there is an effective treatment
- Additional effect may be too small: High sample sizes
- Drug-drug interaction, additional side effects

Pediatric subgroup

Adult trial with pediatric subgroup

Pros:

- Borrow strength from adults in the same setting
- Within-trial modelling more robust than between-trial modelling

Cons:

- Similar problems as in separate pediatric trials
- Pediatric subgroup may need different conduct than adults: No difference to separate trials

Dose response

Compare to low dose instead of placebo

Pros:

- No placebo needed

Cons:

- Low dose may also be unethical if ineffective
- Large sample size if low dose better than placebo
  - e.g. 4 times higher if low dose half as effective as high dose compared to placebo

Longitudinal data analysis

Use repeated measurements over time in primary analysis

Pros:

- Increased information
- Lower sample size

Cons:

- Rely on model assumptions
- May not focus on relevant time point
- Placebo still required

Possible “requirement easing”

- Increasing reliance on assumptions
  - NI (assay sensitivity, constancy)
  - Withdrawal design (transferability)
  - Surrogate endpoints (validity)
  - Evidence synthesis (prior belief)
  - Extrapolation from adults, PK/PD modelling (model, distributions)
- Increasing false + for less false – ?
- No independent confirmation

Potential paradigm change ?

- Usual Phase III paradigm
  - Proper well defined question to be asked prior to study
  - If generated data incompatible with null hypothesis then a “proof” of is assumed
  - Subjectivity excluded

vs

- Relaxed requirements
  - “reasonable” additional information should be unbiased – unprejudiced: difficult to decide

Summary

- Lowering the burden of study participants requires
  - Either less evidence for future patients
  - Or increasing reliance on assumptions, increasing subjectivity
- “Risk-Benefit of trial design” to be assessed
  - Risk: Decreasing robustness
  - Benefit: Decreasing burden of participants
- Combination of different approaches could help