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## Complexities of conducting clinical trials in rare paediatric disorders



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## Background


- Paucity of child-relevant evidence for medical interventions
- Health care providers frequently extrapolate adult trial results to children
- Optimal care of children requires evidence from high quality paediatric clinical trials
- While high quality RCTs are the gold-standard for determining clinical efficacy, in children there are times when:
  - number of participants is unavoidably small
  - age-appropriate, valid and reliable outcome measures are lacking
  - analysing and interpreting objective/subjective outcomes related to growth and development over time are complex
  - ethical concerns preclude enrolment

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## Overview

- Discuss some problems associated with conducting clinical trials in children with rare diseases:
  1. Recruitment
  2. Outcomes
  3. Data analysis
  4. Ethics
- Clinical context: Neuromuscular disorders
  - Ascorbic acid for Charcot-Marie-Tooth disease ( $n=81$ )
  - Deflazacort for Duchenne muscular dystrophy ( $n=10$ )
  - Lovastatin for Neurofibromatosis type 1 ( $n=140$ )
  - Curcumin for Dejerine-Sottas Syndrome ( $n=3$ )
  - Botulinum toxin-A for cavus foot deformity ( $n=10$ )
  - Stretching ankle contracture in neuropathy ( $n=30$ )
  - PTC-124 for Duchenne muscular dystrophy ( $n=160$ )



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## 1. Recruitment

- Many successful paediatric trials deal with more common disorders (e.g. Asthma) where adequate samples for recruitment are possible ( $n=600-1000$ )\*
- Often the number of participants is unavoidably small in rare paediatric disorders ( $n=10-100$ )
- Diagnostic difficulty for inclusion of children with rare diseases, therefore ineligibility upon further investigation
- Greater trial costs due to multiple attendees (travel/accommodation), staff expertise, geographical expanse, palatable formulation
  - Small market = need vs. profit (can become unprofitable)

\*Peat JK, et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. Journal of Allergy and Clinical Immunology 2004; 114: 807-813.

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## 2. Outcomes


- Lack of age-appropriate, valid and reliable outcome measures
  - many diagnostic tools not validated to measure change and are not sufficiently sensitive to determine treatment effect
- Children are moving targets
  - each age brings physiological and cognitive developmental challenges
  - tests must be standardised across age groups (ceiling & floor effects)
- Children bore easily and can react very badly with pain (e.g. blood test), especially with behavioural co-morbidities
  - negative impact on participant-centred outcome measures
- Length of assessment
  - time constraints (limited concentration)

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## 2. Outcomes: Objective

- Children are not small adults
  - differ in physiology, biology, disease progression, response to intervention, potential risks, etc
- Effect of child growth and development on physical outcomes (e.g. strength) pose a number of statistical challenges
- To ensure adequate power, must use outcomes that are (or can be made) independent of age, body size and cognitive development
  - e.g. in a sample of 2-16 year olds, there is great variance from one child to the next both across and within age strata
- Require clean, fast and easy to obtain outcomes
  - quantitative muscle strength, ankle range, nerve conduction



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## 2. Outcomes: Subjective

- Objective endpoints often lack clinical relevance
  - subjective measures such as pain, disability and happiness may be more important to parents
- Child self-report
  - Appropriate age? Developmental delay?
  - Direct measure of pain/disability in young children not reliable
- Parent/proxy report
  - Subjective outcomes prone to bias if parent-reported
    - may not always reflect the child's own situation
- Should child or parent-report be used as primary outcome?
  - Which is more accurate?
  - Need for standardisation across sample i.e. relevant for 2-16 years
    - lead to multiplicity concerns in analysis

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## 3. Data analysis and interpretation

- Analysing and interpreting objective and subjective outcomes related to growth over time are complex
  - normalise to dimensionless variables wherever possible (Stansfield, 2003)
- While binary outcomes (e.g. episode incidence) are easier to interpret, continuous outcomes (e.g. muscle strength, pain level, IQ) are often collected with all the associated statistical angst
  - error: random error (SEM) and regression to mean
  - many statistically improved patients remain symptomatic/impaired
  - clinical vs. statistical significance

Stansfield, et al. Normalisation of gait data in children. Gait Posture 2003; 17: 81-7.

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## Clinical vs. Statistical Significance

Burns J, Ryan MM, Ouvrier RA. Evolution of foot and ankle manifestations in children with CMT1A. Muscle & Nerve. (in press).

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## 4. Ethics

- Ethical considerations can preclude enrolment and bias results
  - in rare diseases, children are often over-researched
- Informed consent/assent
  - child vs. parent motivation
    - unlike adult trial participants, children seldom volunteer for a trial, but are strongly 'encouraged' by their parents to participate
    - impacts on child-based outcomes and adherence to intervention
- Experimental intervention concerns
  - risk : benefit ratio
- Placebo trial-arm in guarded prognoses
- Time to conduct measures in children who are severely disabled
  - burden on family of many medical appointments
  - impact on learning by missing school

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## Conclusion

- Urgent need to increase the number of clinical trials targeting rare diseases of childhood and adolescence
- Conducting trials in rare paediatric diseases will always be complex due to limited financial returns, standardising outcomes, difficulty analysing and interpreting paediatric data and ethical concerns about consent and toxicity
- There may be solutions to many of these dilemmas such as multicentre involvement, pooling of resources, expertise in consortia, and even alternate study designs
- Cures *are* on the horizon and they *are* worth chasing

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## Thank you

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