

Discussion: Sildenafil case

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- Similarity of disease?
- Similarity of response to treatment?
 - Pathophysiology; pharmacology
 - Historical data
 - Evolving data

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Pharmakokinetics:

- Could the initial dose-projection be improved
 - Physiology-based model
 - Separate PK study
 - Age-staggered approach
- Dosing by weight categories (8-20; 20-45; >45kg) rather than individual weight-adjusted dosing
 - high variability of actual doses and overlap between dose categories
 - Analysis by actual doses/exposures?
- Lack of age-appropriate formulation
- Age-groups ignored

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Endpoint correlations (translation):

Literature: 6MWT ~ morbidity & mortality (adults)

Literature: CPET ~ morbidity & mortality (adults)

Literature: 6MWT ~ CPET (some limitations) (adults and children)

FDA/Sildenafil: 6MWT ~ PVRI (adults)

Sildenafil: CPET ~ PVRI (children) ?

6MWT ~ PVRI_{adults} = CPET ~ PVRI_{children} ??

data in children unable for CPET ?

- Approach generally supported but not all assumptions validated
- Measure further endpoints in parallel (TTCW, echo, BNP, etc)
- Further validation across several trials/drugs