Issues in Pediatric Research

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Group 1:  
= 28 days postop  
(N=84)  

Group 2:  
= 6 mo postop  
(N=265)  

Screened for Trial  
(N=349)  

At least mild to moderate MR *  
(N=139)  

(by local echo)  

Potentially trial eligible (N=54)  

ACE inhibitor use  
(N=47)  

Associated complex defect  
(N=8)  

Other clinical exclusion (N=17)  

Not approached  
(N=13)  

(by core lab echo)  

Less than moderate MR  
(N=42)  

Unknown MR  
(N=3)  

At least moderate MR **  
(N=9)  

Residual shunt  
(N=1)  

Trial eligible & no exclusion criteria  
(N=8)  

Randomized  
(N=5)  

* Qualitative assessment  
** Quantitative assessment  
MR, mitral regurgitation
A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging, Parallel Group Study of Intravenous Sildenafil in the Treatment of Children, Aged 0 to 17 with Pulmonary Hypertension After Corrective Cardiac Surgery Protocol Number: A1481134

Randomisation of subjects was to be stratified by age (neonate or non-neonate) and by study centre. They were to be randomized 63 patients per group, however only 18 patients were randomized.

DSMB stopped study for futility: Study would take 18 years to reach target enrollment.
Children are Not Small Adults

- Developmental changes in biology
  - Absorption, distribution, binding, clearance of drugs are age-dependent

- Ability to deliver therapy in children
  - Liquid formulation
  - Dietary differences

- Extrapolated dosing may not account for physiologic and metabolic differences in children
Pediatric drug therapeutics

- Historically, 75% of drugs have insufficient labeling information for pediatric dosing, safety, or efficacy.
- Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits.
Pediatric Regulatory Changes

The Pediatric Rule
FDA allows pediatric labeling based on extrapolation of efficacy from adults + PK/PD data in children.

The Final Rule
FDA requires pediatric studies of new products, indications, dosing regimens, etc.

A U.S. federal judge strikes down the Final Rule deciding that FDA does not have authority to require testing in children.

FDA Modernization Act (FDAMA)
Provides 6-months extended market (pediatric) exclusivity for drugs studied in children.

Best Pharmaceuticals for Children's Act (BPCA)
Reauthorizes pediatric exclusivity with provisions for study of off-patent drugs including development of the priority list.

Pediatric Research Equity Act (PREA)
Congress codifies the Final Rule requiring pediatric study of new products.

FDA Amendments Act (FDAAA)
Reauthorizes pediatric exclusivity and revises priority list to emphasize therapeutic areas of need.

FDA Safety and Innovation Act (FDASIA)
BPCA/PREA reauthorized without sunset.

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Trials in children are costly and inefficient


- Median trial enrollment: 140 subjects
- Median # of case report forms: 74
- Median time to completion: 2 years
- Median cost
  - Multi dose PK study: $2.3 million
  - Efficacy study: $6.5 million
Burdens of the Clinical Investigator in Pediatric Populations

- Disease diversity => Limits sample size => Hard end-points are frequently not achievable => Surrogate end-points are required
- “Small” market limits financial support options
- Informed consent in this “vulnerable population” requires higher confidence of potential benefit and relatively smaller risk
- Therapies are often adopted early based on preliminary evidence of efficacy and “clinical equipoise” is very transient
- Clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial
Additional considerations in pediatric drug Randomized Clinical Trial

- Local practice vs. standard of care
- Concerns about placebo
- Children cannot experience more than minimal risk without benefit
- Clinical equipoise
- Paradox in pediatrics
  - Most drug use in “routine clinical care” is off-label
  - Oftentimes more acceptable to physicians, parents, and IRBs to use untested medications in routine clinical care than to enroll a child in a RCT
Pediatric Endpoints are a Challenge

It is hard to demonstrate that children have higher mortality or more morbid events

- Rare diseases
- Low mortality rates
- Relatively rare serious medical events
- Heterogeneous management
- Extrapolation from adult data can be misleading
- Inadequate power.
Some outcomes of intervention in childhood may not be apparent until many years later.
Surrogate End-Points

- Use of surrogate end points can reduce the size, duration, and cost of clinical trials
- Strongly endorsed by patient advocacy groups and industry
- To be useful, the treatment effects on the surrogate end point must reliably predict the treatment-induced effect on clinical efficacy
You may have only 1 opportunity for a pediatric study

- How do we make the most of the opportunity?
- How do we balance competing pressures?
Patient population – who do you enroll?

• Homogeneous
  – Fewer subjects available
  – Higher prevalence of outcome
  – May be easier to show a difference
  – How do we generalize results to other populations

• Heterogeneous
  – More subjects available
  – Prevalence of outcome diluted
  – May be harder to show a difference
  – Generalizability is inherent
We need to TRANSFORM the way we think about pediatric research!
THANKS!