

Pediatric Clinical Trials Workshop

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Unmet Needs in the Pediatric Population: Obstacles to Pediatric Medical Device Research

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Disclosures

- **Consulting/Royalty payments for other products from the same company as the products discussed: Globus Spine, Inc. 2007-08**
- **Research or other financial support from the same company as the products discussed: Chest Wall Spine Deformity Foundation and Synthes Spine, North America**

The Problem

- **Financial and regulatory obstacles limit innovation, research and development specific to the care of pediatric orthopaedic conditions**



Novel, Child Specific, Devices: *Financial Obstacles*

- **Markets are small**
- **Financial incentives weak**
- **Limited sales from any single product**
- **Device life cycle short**
 - Patent protection not strong
- **Liability concerns – performance evaluated over decades**
 - Few if any long term outcome studies



Novel, Child Specific, Devices: *Regulatory Obstacles*

- **Safety and effectiveness for specific pediatric indications not formally evaluated**
 - **510(k) approval not applicable to modification of existing device used for pediatric indications**
 - **Safety + efficacy data from adults may not be extrapolated to children – different anatomy, physiology and pathology**
- **IDE or PMA for specific pediatric indication required**



Methodological Challenges to Pre-market trials and Post-market Surveillance

- Prospective, randomized, controlled studies (RCCTs)
 - costly, technically challenging, arduous
- IRBs will not approve RCCTs that evaluate “off-label” use of a medical device - unless part of IDE
- Rare diseases = small sample size
- Difficulty establishing appropriate control groups
 - randomization to “untreated” (natural history) control ethically unacceptable or rejected by parents
 - no universally accepted “gold standard”
- Non-linear somatic growth and development in children affects measurement of anatomical and functional outcomes

Financial challenges to Pre-market Trials and Post-market Surveillance

- **↑ cost design, engineering and manufacture of pediatric orthopaedic devices**
 - **↑ Range of sizes, must accommodate growth, may require long term durability**
- **Devices approved for use in adults can legally be used in children (physician directed)**
 - **Limited financial incentives for Industry to fund IDE to evaluate pediatric device indications**



Pathways to Approval: New Devices

Before in-vivo human trials can be conducted:

- Pre-requisite *ex-vivo* mechanical testing (ASTM) to establish performance parameters
 - Surrogate models must replicate wide range of anatomy/geometry, growth and longer durability
- Pre-requisite *in-vivo* animal studies to establish safety, efficacy of device in proposed application
 - May be difficult to establish clinically relevant model
 - Model may not replicate human disease etiology, physiology or pathology but still useful for evaluating mechanical performance and safety

Pathways to Approval: Human Trials

Challenges and Solutions

- *Regulatory mechanisms must balance need for innovation with reasonable assurance of safety and efficacy*
- **RCCT = Gold Standard**
 - Costly, arduous, technically complex, long time
 - Small patient populations = limited statistical power
 - Patients, families refuse to accept randomization
- **Develop alternative approval pathways that establish assurance of safety + efficacy**
- **Provide financial incentives to Industry to develop & test pediatric devices in clinical trials**

Develop Framework to Conduct Prospective Evaluation of Physician Directed Uses of Medical Devices (not part of IDE)

- **NIH / FDA establish criteria for IRBs to approve prospective, *in-vivo* studies that assess safety and efficacy of physician directed applications of devices approved for adults to be used in children**
- **Establish mechanism of extra-mural funding for independent, non-industry sponsored research**
 - **Grants reviewed and administered by NIH to assure independence, integrity and lack of bias**
 - **Funded by pooled contributions from medical device industry (Advamed)**

Alternatives to RCCT

Beekman et al. Pediatrics 2009; 124; e155-162

- **Use of Objective Performance Criteria and Performance Goals**
- **Extrapolate existing data from studies of adults to establish equivalent performance in children**
- **Use data collected prospectively by Multi-center Study Groups and Registries**
- **Enhanced post market surveillance**
- **Use of Data generated outside of USA**



Objective Performance Criteria and Performance Goals

- Less demanding alternative to RCCTs
- Provides “control group” for non-randomized clinical trial
- Establishes minimally acceptable value or benchmark in *ADVANCE* of prospective study to determine if device application is effective and safe
- Metrics derived from historical data – pooling of previously published studies w/ appropriate statistical modeling and analysis



Extrapolate Data from Studies Conducted in Adults

- Adult device application similar to pediatric application
- Ex-vivo : evaluate mechanical performance in surrogate models simulating use in children
 - mechanical tests conducted using cadavers (animal and/or human) under conditions simulating clinical application of device in children
 - theoretical evaluation using analytical methods (finite element analysis)
- In-vivo: performance data from adults extrapolated to pediatric applications

Use of Study Groups and Registries

- Requires well defined data set
- Prospective, sequential patient enrollment
- Consistent inclusion/exclusion criteria
- Standardized follow-up
- Uniform, independent assessment of clinical, radiographic, and patient centered outcomes
 - Clear criteria to assess success or failure
- Longitudinal follow-up → post-market surveillance
 - must account for ALL patients treated with device,
 - detail all complications
- Minimal amount of missing data

Enhanced Post Market Surveillance

- In exchange for enhanced post-market surveillance, FDA accepts safety and efficacy data from smaller studies with shorter follow-up to qualify devices for conditional approval
- Final or unconditional approval granted after post-market studies are completed and demonstrate acceptable safety and efficacy outcomes



Use of Data Generated Outside USA

- High quality, well controlled and well monitored studies performed outside of the US could provide support for pre-clinical trial approval or take place of US feasibility study
- Qualify devices for conditional approval with enhanced post-market surveillance



Conclusion

- **Novel regulatory pathways that accommodate the realities and challenges of developing medical devices specific to the care of pediatric orthopaedic conditions and facilitate rather than inhibit clinical research are required to foster innovation but must also safeguard the needs of vulnerable children**



Thank you

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