Clinical Trials in Children
Importance of Clinical Trials in Children

• Lack of trial-based data forces extrapolation
  – Different diseases, different mechanisms
  – Metabolism is different, unpredictable
  – Unforeseen consequences child-specific
    • Reye’s syndrome with aspirin
    • Staining of teeth with tetracycline
    • Phycomelia with thalidomide
  – Only 54% drugs in PDR tested
Some Reasons Why Not

- Industry-market forces/liability/jeopardy
- Lack of FDA enforcement/waivers
- Potential difference in EMA and FDA
- Government-minimal funding for NICHD
- Patients’ parents/work/parent disagreement
- Patients
  - Unable to give consent/failure to continue once 18y
  - Difficulty understanding assent
  - Limited understanding of research benefit
  - Procedural fear
More reasons.....

- Clinicians
  - Content to extrapolate
  - Lack of funding/central resources
  - Risk aversion
  - Lack of training
  - Lack of networks
  - Indemnity concerns of hospitals
<table>
<thead>
<tr>
<th>Legislation</th>
<th>Year</th>
<th>Provision</th>
<th>Scope and Implementation</th>
</tr>
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<tbody>
<tr>
<td>Best Pharmaceuticals for Children Act</td>
<td>2002</td>
<td>Extends market exclusivity for 6 months for sponsors who voluntarily complete studies involving children according to specified terms and timelines outlined by the FDA in written requests</td>
<td>The FDA may issue written requests for studies involving children regarding approved and unapproved indications pertaining to products still under initial development or those already marketed. The exclusivity is granted for an active ingredient and applies to all FDA-approved products (and their approved indications) containing the ingredient. Exclusivity is granted to sponsors who meet the terms of the written request, irrespective of whether safety and efficacy in children are shown.</td>
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<tr>
<td>Pediatric Research Equity Act</td>
<td>2003</td>
<td>Authorizes the FDA to require sponsors to perform studies involving children to assess the safety and effectiveness of a drug or biologic product for the claimed indications in all relevant pediatric subpopulations; also requires sponsors to provide information regarding dosing and administration for each pediatric subpopulation for which the drug or biologic is safe and effective, before it is marketed</td>
<td>Requirements pertain to applications (or supplements to an application) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration for all drug and biologic agents, unless the FDA issues a waiver or deferral for some or all studies involving children. Requirements do not pertain to indications for which an Orphan Drug Act designation has been granted. Studies involving children can be requested only for the indications that are under review in adults.</td>
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<tr>
<td>Rare Pediatric Disease Priority Review Voucher Incentive Program</td>
<td>2012</td>
<td>Authorizes the FDA to grant priority-review vouchers to sponsors who receive approval for a product to treat rare diseases in children</td>
<td>A voucher can be redeemed to receive a 6-month priority review of a subsequent marketing application for a different product that would have qualified only for 10-month standard review, including products intended only for adult use. Vouchers may be transferred, including by sale, for use by other sponsors.</td>
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**Effect of PREA and BPCA on Drug Labelling for Children**

**Figure 1.** Labeling Changes for FDA-Approved Drugs for Children.

From 1998 through 2018, there were 770 labeling changes pertaining to children for 620 unique products. From 2014 through 2018, a total of 9.5% (24 of 253) of these changes were attributed to the Best Pharmaceuticals for Children Act (BPCA), 73.9% (187 of 253) to the Pediatric Research Equity Act (PREA), and 16.6% (42 of 253) to both the BPCA and the PREA. The Pediatric Rule, the precursor to the PREA, was in effect from 1998 through 2002. Data are from the New Pediatric Labeling Information Database of the Food and Drug Administration (FDA)."
Benefits of trial participation

• Access to new/better/novel treatments
• Affordability
• Clinical scientists more likely to incorporate optimal tx
• Inclusion benefits for all trial participants (Hawthorn effect, placebo>non-participants, survival advantage, more attention/work-up)
  – Why is this?
Risks of Trial Participation

- Discomfort
- Fear
- Separation from parents
- Size or volume of clinical samples
- Unknown developmental effects
- Unrecognized adverse consequences
What constitutes acceptable risk?

**Therapeutic:**
Higher risk allowed for potential benefit of amelioration

**Non-therapeutic:**
Prevention
Screening
Side-effect monitoring
QOL or questionnaires
Public Policy and Child Research

• Regulatory
  – 1998 NIH requires human subject research by NIH funds to include children
  – 1998 FDA Pediatric Rule requires RCT in children before approval of use in children
  – Rare Disease Priority Act (2012)
    • 6-month review instead of 10 months
Ethics of consent for children

- Consent by proxy makes parents less likely to consent than if for themselves
- Assent can be overridden by parental consent
- Payment for participation/coercion
- Payment to recruiters to trials
- Grant support for researchers
IRB concerns

- Under-resourced
- Overburdened
- Unduly focused on procedural aspects
- Insufficient training in child ethics/standards of IRB members
- Right of individual>>>societal benefit
Trials vs. Practice

- Doctors use untested meds and diagnostics as “routine clinical care” in lieu of clinical trial
- Clinical trial subjects regarded as “guinea pigs”
- Sentinel events in clinical trials over-reported as “human experimentation”
- Double-standard where treatments in trial scrutinized > non-standard tx in clinical care
Trials vs. practice

• Should adults be enrolled/completed in clinical trial and results known before child trial?
  – Clinical equipoise
  – Delay in effective treatment for children
  – Insurers deny drug approval for children paid for adults
  – Efficacy extrapolation
  – Formulation/dosing/stability/age range
  – 6 month patent prolongation comes late
Why so few children in clinical trials?

- Smaller pool of patients for recruitment
- Small trials underpowered
- Dose-response difficult due to child size, age, development, gender
- Market generally less robust
- Under-utilized iACT and Pediatric Trial Network
Physician reasons for low accrual rates

- Pediatrician conflict between caregiver and scientist
- Lack of awareness, time, finances, central coordinators
- Lack of rewards or recognition
- Fear of losing patients
- Loss of autonomy
- Distrust of researchers/research
- Cultural/language trust/clarity
Pediatric histology may be unique

Type 1

Type 2/BZ1

Schwimmer, Lavine et al, Hepatology, 2005
Inverse Relation of Classic NASH and Type 2 NAFLD with Age

![Graph showing the inverse relation of Classic Steatohepatitis and Type 2 NAFLD with age. The graph displays the percentage of the population at each age group, showing a decrease in Classic Steatohepatitis and an increase in Type 2 NAFLD with age.](image-url)
Etiopathogenesis and treatment response may depend on pediatric subtype

- Drugs found to be effective in adults may not apply to distinct pediatric (type 2/BZ1) subtype
- Natural history/evolution of disease may vary
- Sex hormone changes surrounding puberty alter histology
- Distinction between patterns only evident by biopsy
- Endpoints for improvement possibly require research-driven biopsy
- Placebo arm of TONIC trial
- Double blind RCT
- Two biopsies
- 47/58 children with 2 biopsies
- Lifestyle SOC 96 weeks
NAS improved by at least 1 point in 55% of children with lifestyle SOC (RCT)

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<th>Characteristic</th>
<th>Coef</th>
<th>95 % C.I.</th>
<th>P</th>
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<td><strong>Baseline:</strong></td>
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<td></td>
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<tr>
<td>ALT (U/L)</td>
<td>-0.006</td>
<td>(-0.014, 0.003)</td>
<td>0.17</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-0.011</td>
<td>(-0.023, 0.001)</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-0.009</td>
<td>(-0.016, -0.003)</td>
<td>0.007</td>
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<tr>
<td><strong>Change at 96 weeks:</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BMI z-score (kg/m²)</td>
<td>-3.64</td>
<td>(1.53, 5.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.053</td>
<td>(-0.106, -0.001)</td>
<td>0.05</td>
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- Characteristics associated with improvement in NAS were **lower baseline AST** and **triglycerides**, and **weight loss** from baseline to end of 96 weeks.
Clinical parameters relating to fibrosis improvement

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<td><strong>Baseline:</strong></td>
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<tr>
<td>Age: 13-17 vs 8-12 yr</td>
<td>-0.50</td>
<td>(-1.17,0.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>Race: White vs non-white</td>
<td>-0.96</td>
<td>(-1.78,-0.19)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI z-score (≥2.5 vs &lt; 2.5)</td>
<td>-0.65</td>
<td>(-1.33,0.021)</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>-0.013</td>
<td>(-0.023,-0.001)</td>
<td>0.03</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>-0.03</td>
<td>(-0.06,0.01)</td>
<td>0.14</td>
</tr>
<tr>
<td>Activity level (MET-hrs/wk)</td>
<td>0.01</td>
<td>(0.001, 0.018)</td>
<td>0.03</td>
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</table>

**Change at 96 weeks:**

No change characteristics were associated

Fibrosis improved by at least 1 stage in 40% of children

- Characteristics associated with improvement in fibrosis were non-white race, lower baseline BMI z-score, LDL cholesterol, higher baseline activity levels
Trial Design Considerations

- Dose/pill v liquid/compliance/stability variants
- Consent/assent considerations/aging out
- Fear of biopsy/blood draws/MRI confinement
- Length of trial
- Benefit/risk re natural history (unknown) v side effects and complications
- Disease severity and “type” 1 or 2
- Possible recruitment difficulty
  - Note EOT liver biopsy usually 85% in two RCT in children
- Inclusion/exclusion criteria
- Primary endpoint(s)-?histology/surrogates?
• Enrollment targets exceeded
• Retention was >86% over 52 or 96 wks
• Research-related percutaneous liver biopsies approved by IRB at all sites, accepted by parents and children
• No serious adverse events from biopsies
• NASH resolution and NAS improvement with vitamin E, but ALT improvement not significant in TONIC
• ALT improvement in CyNCh, but not NAS improvement
• NAS endpoint in Type 2, but not Type 1 NAFLD in CyNCh
What Needs to Be Done?

• Identify cost-effective strategies for screening those at risk
• Develop predictive and validated noninvasive measures for diagnosis, prognosis, monitoring
• Characterize longer term natural history
• Modify genetic and environmental factors responsible for onset and progression
• Identify safe, effective, affordable therapy(ies)