Goals, Objectives & Workshop Format

Ed Connor, MD, MBE, FAAP
Chairman and Interim Chief Medical Officer
I-ACT for Children
Institute for Advanced Clinical Trials for Children

- An independent 501(c)3 public-private collaboration to advance innovative medicines, device development and labelling to improve child health
- Focus on innovation, efficiency, quality, child-health impact
- Funded by membership, FDA U018 grant, donations/philanthropy
- Work in pre-competitive and proprietary space as an independent non-profit
- Neutral forum engaging diverse stakeholders
- Pre-competitive work focuses on priority areas of innovation in drug development

**Vision:** We act because every child with a medical need deserves the best chance possible. That chance depends on a commitment to innovation, quality and urgency in advancing medical therapies specifically for children.
Institute for Advanced Clinical Trials for Children

**Strategy & Planning**

- Quality and Efficiency
  - Innovative trial design
  - Site feasibility assessment
  - Independent assessment of programs/strategy including PIPs, PSPs, protocols
  - Protocol optimization
  - Use of real-world data

- Access and Global Reach
  - Geographically diverse centers of excellence
  - Pre-qualified sites
  - Patient recruitment strategies & materials
  - Efficiency metrics, troubleshooting, training

**Tools, Capabilities, Best Practices**

- Consistency and Competency
  - Standard processes & practices
  - Site optimization
  - Centralized ethics review
  - Pediatric-based GCP & other education

**Infrastructure & Trial Execution**

- Thought Leadership
  - Engaging stakeholders to generate discussion, launch groundbreaking initiatives
  - Shaping an environment that embraces the need for/adoPTION of trial innovation
Adolescents in Adult Clinical Trials

• Innovation in clinical trials is essential to advancing the development and labeling of new medicines for children
• Use of innovative methodology provides the opportunity to catalyze development while maintaining quality
  o Extrapolation, trial simulation, mechanism-based drug development, adaptive design, master protocols/platform trials, real-world data, inclusion of adolescents in adult trials
• While considerable interest, enthusiasm and rationale exist for inclusion of adolescents in adult trials, several important issues need to be addressed
• This workshop is organized by I-ACT for Children’s Coordinating Committee, informed by discussions with stakeholders and initiated by a workshop held by BIO and the academic community

**Working Assumption:** *When appropriate*, adolescents should be included in adult trials of innovative drugs.
Adolescents in Adult Clinical Trials

- **Focus**: Scientific, bioethical and operational issues in trials designed for registrational purposes
- **Goal**: Identify major gaps and proposed solutions
- **Process**: Moderator/panel format on DAY 1 to lay out the issues/solutions, followed by working sessions on DAY 2 to develop issues/solutions in more detail and then summary of deliberations
- **Outcome**: Materials for preparation of white paper/meeting proceedings

**Perspective**
- ✓ Product development context...
- ✓ Delineation of dependencies...
- ✓ Practical advice and guidance...
- ✓ Solutions-oriented report...
# AGENDA: Adolescents in Adult Clinical Trials

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td><strong>DAY ONE</strong></td>
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<tr>
<td>11:30 am</td>
<td>Working Lunch</td>
</tr>
<tr>
<td>Noon-12:15 pm</td>
<td>Goals, Objectives, Workshop Format</td>
</tr>
<tr>
<td>12:15-1:15 pm</td>
<td>Background, Current Landscape &amp; Gaps</td>
</tr>
<tr>
<td>1:15-2:15 pm</td>
<td><em>Panel 1:</em> Scientific, Trial Design &amp; Analytical Issues &amp; Potential Solutions</td>
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<tr>
<td>2:30-3:30 pm</td>
<td><em>Panel 2:</em> Bioethical Issues &amp; Other Adolescent-Specific Factors</td>
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<tr>
<td>3:30-4:45 pm</td>
<td><em>Panel 3:</em> Operational Challenges, Lessons Learned &amp; Proposed Solutions</td>
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<tr>
<td>4:45-5 pm</td>
<td>Day 1 Summary</td>
</tr>
<tr>
<td>5-5:15 pm</td>
<td>Framework &amp; Working Group Assignments, Objectives for Day 2</td>
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<tr>
<td>6 pm</td>
<td>Dinner and Speaker</td>
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<td><strong>DAY TWO</strong></td>
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<tr>
<td>8-8:30 am</td>
<td>Breakfast</td>
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<tr>
<td>8:30 am-Noon</td>
<td>Working Group Sessions</td>
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<tr>
<td>Noon-1 pm</td>
<td>Working Lunch</td>
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<tr>
<td>1-4 pm</td>
<td>Presentation of Final Draft Framework &amp; Recommendations</td>
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<tr>
<td>4-4:30 pm</td>
<td>Summary, Closing Remarks &amp; Next Steps</td>
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Background, Current Landscape & Gaps

Christina Bucci-Rechtweg, MD, Novartis
Carmen Moreno, MD, PhD, conect4children
Lily (Yeruk) Mulugeta, PharmD, FDA
Collin Hovinga, PharmD, I-ACT for Children
The Current Regulatory Environment

How do we define “adolescent?”

Christina Bucci-Rechtweg, MD, Novartis
Conflict of Interest & Disclaimer

- The presenter is an employee of Novartis Pharmaceuticals Corporation (‘Novartis’)

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Regional Pediatric Regulatory Requirements

- Pediatric regulatory policy in US and European markets have been primary drivers of pediatric drug development

- However, more company pipelines include evaluation of novel medicines for pediatric use
  - In 2018, 30% of NME approvals in the US included “Pediatric Indication for Use”
Regulated drug development is global.

ICH regulatory regions now include:
- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan
- Health Canada, Canada
- Swissmedic, Switzerland
- ANVISA, Brazil
- MFDS, Republic of Korea
- HSA, Singapore
- NMPA, China
- TFDA, Chinese Taipei

Standing Observer: WHO
## Regulatory Definitions for Adolescent: US

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Definition</th>
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<tr>
<td>FDA, United States</td>
<td>In the 1994 rule, FDA defined ... adolescents as 12 years to 16 years (59 FR 64242). .... The metabolism and elimination of the drug and the stage of development of the child may be important in determining which age groups should be tested. ...¹</td>
</tr>
<tr>
<td></td>
<td>(b) Age categories. When we determine whether you are functioning independently, appropriately, and effectively in an age-appropriate manner, we will consider your age in the following categories: ... (3) Children (age 3 to attainment of age 18), considered according to the following subcategories: ... (iii) Young adolescents (age 12 to attainment of age 16), and (iv) Older adolescents (age 16 to attainment of age 18).²</td>
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<td>Pediatric medical devices treat or diagnose diseases and conditions from birth through age 21. The Federal Food, Drug, and Cosmetic Act (FD&amp;C Act) defines pediatric patients as persons aged 21 or younger at the time of their diagnosis or treatment. Pediatric subpopulations are further categorized as follows: ... Adolescents - aged 12 through 21 (up to but not including the 22nd birthday)³</td>
</tr>
</tbody>
</table>

¹Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products; Proposed Rule (21 CFR Parts 201, 312, 314, and 601); ²20 CFR 416.924a – ‘Age as a factor of evaluation in childhood disability’; ³Section 520(m)(6)(E)(i) of the FD&C Act
Regulatory Definitions for Adolescent: Europe

<table>
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<tr>
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<tr>
<td>EC, Europe</td>
<td>The paediatric population encompasses several subsets, as defined e.g. in international guidelines: adolescents from 12 up to 18 years. However, when it is considered more appropriate to use different subsets (e.g. based on gender or stage of pubertal development), this may be acceptable, but the choice of subsets should be explained and justified.(^1)</td>
</tr>
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<td></td>
<td>In accordance with current guidelines, the applied age classification of paediatric patients is: adolescents: from 12 years to less than 18 years(^2)</td>
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\(^1\) EC Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01); \(^2\) Guideline on good pharmacovigilance practices (GVP) – P. IV EMA/572054/2016
# Regulatory Definitions for Adolescent: ROW

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<tr>
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<tr>
<td>Health Canada, Canada</td>
<td>The Canadian Paediatric Society believes that a definition of adolescence based solely on chronological age is unjustified and impractical. The Society favours a more functional definition based on the biopsychosocial readiness of young people to enter adulthood. Adolescence begins with the onset of physiologically normal puberty and ends when an adult identity and behaviour are accepted. This period of development corresponds roughly to the period between the ages of 10 and 19 years, which is consistent with the World Health Organization’s definition of adolescence.¹</td>
</tr>
<tr>
<td>MHLW/PMDA, Japan</td>
<td>The Civil Code of Japan provides that anyone who has attained the age of 20 may conduct juristic acts independently. Therefore, all contracts or agreements on medical treatment entered into by a person under 20 years of age without the consent of his/her legal representative may be canceled by the legal representative, though such contract or agreement remains effective retained if not canceled by the legal representative.²</td>
</tr>
<tr>
<td>NMPA, China</td>
<td>Eighteen is the age of majority in China. Under the Minors Protection Law, “minors” are defined as citizens less than eighteen years old. The civil law of China provides that people above eighteen years old and those from sixteen to eighteen who make a living on their own have full civil conduct capacity. People aged from ten to eighteen have limited capacity of civil conduct and may only engage in civil activities appropriate to the age range and intellect. People under ten years old have no civil conduct capacity. Unless otherwise indicated, “children” or &quot;minors&quot; hereinafter refers to people under the age of eighteen.</td>
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¹Age Limits and adolescence. Paediatr Child Health. 2003 Nov; 8(9): 577; 2 The Ministry of Foreign Affairs of Japan - II. ARTICLE 1 (Definition of the child) B. Age limitation applied to legal competency in Japan; ³The Minors Protection Law, art. 2
### Regulatory Definitions for *Adolescent*: International

<table>
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<tr>
<th>Jurisdiction</th>
<th>Definition</th>
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| **ICH E11 (Section 2.5.5)** | 12 to 16-18 years (dependent on region)  
This is a *period of sexual maturation*; medicinal products may interfere with the actions of sex hormones and impede development. In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate.  
This is also a *period of rapid growth and continued neurocognitive development*.  
Medicinal products and illnesses that delay or accelerate the onset of puberty *can have a profound effect on the pubertal growth spurt* and, by changing the pattern of growth, *may affect final height*. *Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies*.  
Many *diseases are also influenced by the hormonal changes around puberty* (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes *may thus influence the results of clinical studies*. |
| **WHO** | Adolescence begins with the *onset of physiologically normal puberty* and ends when an adult identity and behavior are accepted. *This period of development corresponds roughly to the period between the ages of 10 and 19 years*... }
Themes Underlying Regional Adolescent Definitions

- **AGE OF MAJORITY**
- **BEHAVIORAL CONSIDERATIONS** - BIOPSYCHOSOCIAL
- **DEVELOPMENTAL CONSIDERATIONS** - PUBERTAL - COGNITIVE - EMOTIONAL
As part of the responsibility to provide better medicines for children, the EFGCP strongly recommends:

- That researchers, regulators, and members of ethics committees weigh the totality of physiologic, pathologic and other disease-specific evidence to consider adolescent inclusion in adult research and vice versa – young adults as an extension population in paediatric/adolescent studies – when relevant as a trial methodology to facilitate earlier access to investigational and approved medicines for adolescent patients.
## Priority Projects

<table>
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<tr>
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<th>Top Priorities</th>
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<tr>
<td>1</td>
<td>Meta-analysis for publication on the experience of hybrid trials (adult and adolescents), existing guidance in the EU/US and impact on product registration(s)</td>
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<tr>
<td>2</td>
<td>Retrospective analysis of the executed EU paediatric investigation plans (PIPs) to analyze algorithms to identify scenarios where similar safety/efficacy data among adolescents and adults may be used as part of the development considerations for similar mechanisms of action</td>
</tr>
<tr>
<td>3</td>
<td>International alignment of approach to facilitate global acceptance of adolescent inclusion in adult research</td>
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<tr>
<td>4</td>
<td>Define pre-requisites/minimum requirements/key criteria for risk-benefit evaluation to support inclusion of adolescents in adult studies (general vs. indication-specific)</td>
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Thank You

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Inclusion of Adolescents in Adult Trials: Rationale and Case Studies

Carmen Moreno, MD, PhD
SERMAS, Hospital Gregorio Marañón, Madrid
ECNP Child & Adolescent Psychopharmacology Network
C4C: A Pan-European Clinical Trial Network

Vision: Better medicines for babies, children and young people through a pan-European clinical trial network

A project under the EU Innovative Medicines Initiative (IMI)

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777389. The Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA”
c4c will use a coordinated approach to deliver high-quality “regulatory grade” clinical trials in:

- Multiple countries
- Multiple sites
- All paediatric age groups

By supporting:

- Trial implementation using resources shared between studies
- Trial design through a combination of information about natural history, feasibility, appropriate innovation and expert opinion.
- Education and awareness within and beyond the network
Key Objectives

- Input in clinical trial design and implementation from pilot expert advisory groups
- More efficient trial implementation through the set-up of national hubs and qualified sites
- Identification of data standards and performance metrics
- Educational programme for health professionals and awareness raising campaigns for the general public
- Business cases for sustainability beyond IMI funding
Key Features

• International network with lean central coordination
• A single point of contact (one-stop shop)
• Efficient implementation of trials
• Consistent procedures across sites
• Strategic and operational feasibility assessment
• Involvement of experts to develop innovative trial designs and methodology
• Multi-KEY stakeholder collaboration
The c4c Consortium Members

• 10 EFPIA companies
• 19 paediatric national networks established (Iceland and Finland one single network)
• 3 paediatric national networks under negotiation
• 2 large patient advocacy groups
• 8 EU multinational specialty networks
• 3 global research networks
• 200 large children’s hospitals

To know more about the c4c Consortium, visit: www.conect4children.org
A private-public partnership between academia and pharma
Strategic Advice

- Innovative methodology experts
- Clinical experts
- Patient participation groups

Study design
Statistics
E-Health
Modelling

Oncology
Psychiatry
Neurology
Intensive care

Patients
 Parents
YPAG
CYP

Coordinated by Secretariat
Create Charter (4.5): Definition of operations and selection of expert members

Strategic feasibility groups

Requests

Advice
- Singling
- Single/multiple hp development
- Clinical Methodology
- Feasibility assessment

Innovative methodology experts
Clinical experts
Patient participation groups

White papers
Multistakeholder meetings
Tools for patient involvement
Rationale for Including Adolescents in Adult Trials

• Similarity between adolescent- and adult- disease, physiology and drug exposure
• Different diseases but with similar targets across age spectrum
• Mechanism of action: Identical drug targets in pediatric and adult populations
  • Consider role of development and maturation: e.g., Brain neurotransmitters, therapeutic windows
• Therapeutic need & disease epidemiology: unfeasible adolescent-specific trials using a drug with efficacy in adults with same disease
• Developmental toxicities
This approach needs to be be **complementary** to existing paediatric drug development approaches and **should not replace or delay** them.

This approach should not delay activation, completion, reporting and publication of **paediatric** trial results.
**ACCELERATE trial strategy for adolescents and young adults**

<table>
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<tr>
<th>Situations</th>
<th>Solutions</th>
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<tr>
<td>Similar targets present across the age spectrum</td>
<td>To include adolescents from 12 years in adult phase-I trials</td>
</tr>
<tr>
<td>Disease similar in adult and paediatric population</td>
<td>To include both paediatric and adult population from phase-II to phase-III trials</td>
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<tr>
<td>e.g. bone sarcoma, Hodgkin disease</td>
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<tr>
<td>Adult disease rarely present in adolescents</td>
<td>To include adolescents from 12 years in adult phase-I to -III trials</td>
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<tr>
<td>e.g. carcinoma, melanoma</td>
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<tr>
<td>Paediatric disease rarely present in the adult population</td>
<td>To include adult patients in pediatric phase-II to -III trials</td>
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<tr>
<td>e.g. medulloblastoma</td>
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To facilitate regulatory authorisation of a given cancer drug for adolescents from 12 years at the same time as adult authorisation

Gaspar et al., 2018
Examples: Duloxetine in Major Depressive Disorder

Emslie et al., 2014
Examples: Divalproex Acid in Bipolar Mania

Fig. 2 Mean change in Young Mania Rating Scale total scores during double-blind (LOCF: n = 70, placebo; n = 74, divalproex ER) and long-term studies (LOCF: n = 54, divalproex ER). LOCF = last observation carried forward.

Wagner et al., 2009
Examples: Quetiapine in Bipolar Depression

Findling et al., 2014

193 patients randomized to treatment, 144 patients completed the study:
75.3% of quetiapine XR group (n=70) 74.0% of placebo group (n=74)
Clinical Pharmacology

• Developmental stages in receptor (target) biology
• Dosing
• Differences in pharmacokinetics due to differences in size and maturation, differential impact of the disease on organ function, elimination clearance...
• Consider need of prior pharmacokinetic assessment (e.g., drugs with narrow therapeutic index)
• Adolescents require dedicated environment/professionals in specialized centers
• Age-appropriate information and consent process
• Local and national regulation on enrollment of minors in clinical trials
• Design issues (e.g., placebo)
Conclusion

• Inclusion of adolescents in adult clinical trials may be an innovative strategy for some but not all clinical trials involving adolescents

• Consideration of individual situations is warranted
Thank you for your attention

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Expediting Pediatric Drug Development: Inclusion of Pediatric Patients in Adult Trials

Lily Mulugeta, PharmD
Division of Pediatric and Maternal Health

I have no financial interests or relationships to disclose
The views do not necessarily reflect the views of the Food and Drug Administration
Timely access to safe and effective therapies for pediatric patients

- Pediatric development program should provide **timely access to**:
  - **Clinical trials:**
    - Should begin once prospect of direct benefit is determined and overall risk benefit has been considered to allow enrollment of children into a clinical trial
  - **Approved therapies:**
    - Pediatric trials should be completed and assessment of the data submitted concurrently with adults or alternatively, complete enrollment before off-label use makes clinical trials difficult to complete (~2 to 3 years after approval in adults).
    - One potential solution: include pediatric patients into adult phase 3 trials pre-approval; alternatively, pediatric patients can be enrolled in a separate and concurrent trial when appropriate.
Draft FDA Guidance (2019): Inclusion of Adolescent Patients in Adult Oncology Clinical Trials

- Enrollment of appropriately selected adolescent patients in relevant adult oncology clinical trials:
  - Justified given the severe and life-threatening nature of their disease
  - Appropriate dosing considerations
  - Adequate safety monitoring required

- Adolescents may be enrolled in adult trials at any stage for drug development when
  - the histology of the cancer or the molecular target of the drug is relevant to cancers in both adult and adolescent patients

- Systemic exposure and clearance of drugs generally similar in adolescent and adult patients

- Age-related differences in safety data should be considered

FDA guidance [https://www.fda.gov/media/113499/download](https://www.fda.gov/media/113499/download)

- Include adolescents in the **initial adult phase 3 trials or conduct a separate adolescent study in parallel**
  - Strong evidence of disease similarity between adults and pediatrics
  - Similarity in dosing/PK in adults and adolescents
- If enrolled in adult phase 3 trial:
  - **Include adolescents in the primary endpoint analysis**
  - Differences between adolescents and adults are not expected to affect clinical trial outcomes (proportion of adolescents enrolled comparatively small)
  - Analyze adolescent and adult populations separately to help evaluate the consequences of possible differences in behaviors that may affect outcome (e.g. compliance with treatment)

[https://www.fda.gov/media/113319/download](https://www.fda.gov/media/113319/download)

• “The arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study”

• “Depending on the condition and treatment, it may be justifiable to include pediatric subpopulations in adult studies or adult subpopulations in pediatric studies.”

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population
Final FDA Guidance (2018): Timing of Pediatric Studies for Atopic Dermatitis (systemic drugs)

- **Studies in pediatric patients should be initiated early in development**, typically after obtaining initial evidence of efficacy and safety from early phase studies in adults.
- Juvenile toxicity studies should be considered before enrollment of pediatric patients in atopic dermatitis trials.
- Some major safety questions (risk for long-latency or low frequency adverse events, may not be resolved before initiation of pediatric studies)
  - “Given the severity of the disease and risk of disease related progression, and the relative risk-benefit calculus with off-label use of immunosuppressive therapies, it is not generally necessary to have an extensive safety database in adults before initiating pediatric studies.”
- **It is important to study all relevant age groups (down to 2 years)**
  - “A sequential approach (studying older patients first) is only needed if specific information is needed from older age groups” (e.g. PK or specific safety concern, etc.)

Retrospective Analysis of Original Submissions to FDA (2002-2017)

Preliminary results

621 original submissions

- 114 Approvals with a pediatric indication
  - 101 Concurrent approval in adults and pediatric patients
  - 77 Combined adult and pediatric trials
  - 12 Parallel pediatric and adult trials

- 507 adult only approvals
  - 13 Pediatric only approvals
  - 12 Trials with adult or pediatric only*

*Efficacy fully extrapolated from population to another (e.g. ophthalmic products)

Submission to the FDA between January 1, 2002 and September 22, 2017; https://www.accessdata.fda.gov/scripts/cder/daf/
Preliminary Results: Characteristics of Submissions


Breakdown by therapeutic area:
- GI/inborn error products, 15%
- Heme-Onc, 13%
- Neuro, 11%
- Pulm/Allergy/Rheum, 11%
- Other, 33%
Concurrent approval in infants/younger children

Subset of database included concurrent approval in infants and younger children:

- Imaging products
- Rare genetic disorders (e.g., treatment of bile acid synthesis, perinatal infantile juvenile onset hypophosphatemia, Pompe disease, Duchenne muscular dystrophy, cystic fibrosis)
- Topical products (e.g., Acute otitis externa, head lice, impetigo, hyaluronidase)
- Primary pediatric/infant conditions (e.g., RSV, infantile spasms)
- Oncology (e.g., acute lymphocytic leukemia)
- Medical counter measure (e.g., anthrax, internal contamination with plutonium)
- Other (e.g., malaria, atypical hemolytic uremic syndrome)
Sampled database: ~ 50%: orphan indications (rare diseases)

Sample size:
- Varied across programs (range 0 to >1,000 pediatric subjects)
  - Likely based on prevalence of pediatric condition relative to adults, available data from prior program(s), knowledge of the drug class, specific safety signals from early phase adult trials, severity of the disease, availability of other therapies, etc.
  - For sample reviewed, FDA reviews (public) did not discuss how the pediatric sample size was derived

Stratification by age:
- Not discussed in sampled FDA reviews; will require review of study protocol

Analyses:
- Majority included pediatric patients in ITT population for primary efficacy analyses
- Majority included subgroup analyses for efficacy and safety
  - Comparison focused on direction not magnitude of treatment effect
  - Descriptive statistics for safety
Mepolizumab (Nucala®)

- Monoclonal antibody (mAb) directed against IL-5 (1st in class)
- Approved for severe asthma with eosinophilic phenotype (November 2015)
- Three pivotal phase 3 studies, included patients ≥ 12 years
  - Early development did not indicate concerning safety signals
  - Adolescents: N=28 across three studies
    - Point estimates of treatment effect favored mepolizumab (confidence intervals wide)
    - Efficacy extrapolated from adult data based on strong evidence of similar disease characteristics and drug effects in pediatric and adult patients
- Patients 6 to 11 years of age
  - 12-week study (PK/PD) with 12 month open-label extension study to assess long-term safety
Case Example 2: Subsequent indications for same molecule

Perampanel (Fycompa®)

- New molecular entity; AMPA receptor antagonist
- **1st indication:** adjunctive therapy for the treatment of partial-onset seizures
- 3 Phase 3 placebo-controlled, parallel group efficacy, safety and tolerability studies:
  - Two studies evaluated 1 dose level; One study: 3 dose levels
  - **Primary efficacy analyses based on Full ITT Analysis Set (n=1207 including 122 adolescents)**
  - Safety Analysis Set (n=1186 including 121 adolescents)
  - **Subgroup analyses performed both for efficacy and safety in adolescents**
    - Efficacy: “efficacy of Perampanel is in a right direction across all doses in subjects aged 64 years old or younger in all three studies”
    - Safety: “a signal for anger and aggression, particularly in adolescents.”
  - Pop PK analyses on pooled data confirmed similar CL/F in adults/adolescents
Case Example 2: Subsequent indications for same molecule

Perampanel (Fycompa®)

- 2\textsuperscript{nd} indication (2015): treatment of primary generalized tonic clonic (PGTC) seizures in patients 12 years and older
- Safety profile known in adults and adolescents from initial approval (smaller sample size acceptable for safety)
- Single study (Placebo controlled study) with an OL extension in patients 12 yrs and older with uncontrolled PGTC seizures
  - Full analysis set N=162 (N=81 Perampanel; N=81 Placebo)
  - 11\% of subjects were adolescents (\textbf{Perampanel N=11; Placebo N=7})
  - Single dose level (dosing similar to POS)
- Subgroup analysis performed for efficacy: “\textit{effect...generally consistent across demographic subgroups}”
- Subgroup analysis for safety; an additional 6 patients in open label extension
- Pop PK analyses confirmed that clearance is not significantly affected by age
Case Example 3: Pediatric Condition (atopic dermatitis)

Crisaborole (Eucrisa ®)

- **Topical treatment** of mild to moderate atopic dermatitis in patients 2 years of age and older (December 2016)
- Atopic dermatitis **predominantly affects children** but also occurs in adults
- Supported by evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled 28-day trials which included 1522 subjects 2 to 79 years of age
  - 1,313 pediatric subjects were 2 to 17 years of age (86.3% of subjects)
- Initial approval down to 2 years of age
Case Example 4: Insufficient data to support approval

Reslizumab (Cinqair®)

- **New molecular entity;** anti-IL5 mAb
- Approved in 2015 as add-on to maintenance **treatment of patients with severe asthma aged 18 years and older with eosinophilic phenotype**
- 3 trials:
  - 16-week dose-ranging lung function study and two 52-week placebo controlled exacerbation studies in patients 12 years and older (add-on to standard of care)
    - **N=40 adolescents (overall N=1,268 subjects)**
    - No significant difference in the pharmacokinetics of reslizumab was observed by age
- **Subgroup analysis for efficacy:**
  - exacerbation rate higher in adolescent patients
- Subgroup analysis for safety
- Overall, **risk-benefit assessment did not support approval in pediatric patients 12 to 17 years of age.**
Dolutegravir (Tivicay®)

- Adolescent trial (N=23)
  - Conducted in parallel to the phase 3 adult clinical trial
    - Trial confirmed adolescent dose achieves exposures within target range from adults;
    - Activity (viral load) at week 24 provided additional supportive evidence
  - Initial approval for adult and pediatric patients weighing at least 40kg (May 2013)

- Pediatric trial (less than 40kg; N=22)
  - Model-based approach for initial dose selections
  - Weight-based cohorts enrollment
  - Cohorts studied in parallel, not sequential (excluding <15kg)
Conclusion

• Considerations generally similar whether separate parallel study or pediatric patients enrolled in adult phase 3 trial

• The acceptability and design largely depends on what data are needed to establish efficacy, safety and dosing in the target pediatric population and whether the objectives can be achieved in the context of the adult trials (concept not limited to adolescents):
  – Evidence of similarity between adult and pediatric disease
  – Mechanistic understanding to support similarity of response to therapy
  – Evidence of preliminary efficacy in adults
  – Clinical safety data in adults to support enrolling pediatric patients
  – Data to support pediatric dose selection

• Additional considerations:
  – Design of the adult trial appropriate/practical for pediatric patients?
    • Is comparator appropriate? Endpoint similar? Duration of study?
  – Impact on extrapolation to younger pediatric population
  – Operational considerations
Acknowledgments

• Lynne Yao
• Gopichand Gottipati
• Ramy Abdelrahman
• Jeff Florian
• Kevin Krudys
• Yodit Belew
• Aneri Parik (student)
• Tara Altepeter
The Adolescent Landscape

Collin Hovinga, PharmD, MS, FCCP
SVP, Clinical and Scientific Development
I-ACT for Children
Preliminary analyses as of September 2019

ClinicalTrials.gov

• Assessment re: inclusion of adolescents in combined trials?
• How has trial indication influenced the use of combined trials?
• What has been the lower age of inclusion in combined trials?

PCORnet/CHA-PHIS

• How many adolescents (with medical conditions) are available for trials?
• How might our definition of inclusion define the number of potential study subjects per site?
• In the case of combined studies, what indications might be feasible at pediatric hospitals?
Inclusion of adolescents in combined trials?

Total Trials, All Indications (N=318,751)

- Trials including Pediatrics (N=9,480)
  - Phases 1-4, interventional, industry sponsor, child (0-17 years)

Pediatric Medication Trials & Enrollment (N=7,107)

- < 17 years only (N=2,522, 35%) (N=2,147, 40%)*
- Child and Adult (N=4,585, 65%) (N=3,241, 60%)*

Excluded: Withdrawn or suspended studies, vaccine trials

* Industry as the sole sponsor

www.clinicaltrials.gov accessed 9/2019
### Decision to combine: Does indication matter?

#### Percentage of Combined vs Child Only Trials by Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Combined</th>
<th>Child Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>94%</td>
<td>6%</td>
</tr>
<tr>
<td>IBD (452)</td>
<td>69%</td>
<td>31%</td>
</tr>
<tr>
<td>Asthma (408)</td>
<td>78%</td>
<td>22%</td>
</tr>
<tr>
<td>JIA, Arthritis (63)</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>Psoriasis (65)</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>T2D (42)</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Depression, Bipolar (69)</td>
<td>76%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Source: www.clinicaltrials.gov accessed 9/2019*
Lowest age of inclusion in combined trials

Lowest Age for Inclusion in Combined Trials

- **Oncology (285)**
- **IBD (45)**
- **Asthma (237)**
- **JIA, Arthritis (27)**
- **Psoriasis (24)**
- **T2D (13)**
- **Depression, Bipolar (10)**

- <12
- 12
- 13
- 14
- 15
- 16
- 17

www.clinicaltrials.gov accessed 9/2019
How does the definition affect the number of adolescents available for clinical trials?

• PCORnet search
• 9 clinical research networks containing adult and pediatric data
• Dates: 1/1/17 to 6/30/18
• Unit of measurement: Unique patient encounters
• At least 2 visits with the diagnosis required within the assessment period
• Medical conditions
  • Asthma
  • Depression, bipolar disorder
  • Type 2 diabetes
  • Inflammatory bowel disease
  • Juvenile idiopathic arthritis
  • Psoriasis

https://archive.pcornet.org/participating-networks/
### Demographics: Total Population Age Distribution

#### Age Distribution in PCORnet (1/1/17 to 6/30/18)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Diagnosis, Any Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Unique Patients</td>
<td>N</td>
</tr>
<tr>
<td>12-14</td>
<td>1,869,951</td>
</tr>
<tr>
<td>15-17</td>
<td>1,640,543</td>
</tr>
<tr>
<td>18-20</td>
<td>1,340,117</td>
</tr>
<tr>
<td>21-23</td>
<td>1,252,615</td>
</tr>
<tr>
<td>24-64</td>
<td>18,737,193</td>
</tr>
</tbody>
</table>

How many adolescents with medical conditions are available for trials?

Medical Condition by Age **Totals in PCORnet** (1/1/17 to 6/30/18)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asthma</th>
<th>Depression and Bipolar Disorder</th>
<th>Type 2 Diabetes</th>
<th>Inflammatory Bowel Disease</th>
<th>Juvenile Idiopathic Arthritis</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Unique Patients</td>
<td>1,427,959</td>
<td>2,259,315</td>
<td>1,654,611</td>
<td>167,778</td>
<td>583,046</td>
<td>148,091</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>By Age (N, % of patients)</th>
<th>Asthma</th>
<th>Depression and Bipolar Disorder</th>
<th>Type 2 Diabetes</th>
<th>Inflammatory Bowel Disease</th>
<th>Juvenile Idiopathic Arthritis</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-14</td>
<td>155,272</td>
<td>89,772</td>
<td>7,299</td>
<td>5,434</td>
<td>5,685</td>
<td>3,049</td>
</tr>
<tr>
<td>15-17</td>
<td>123,662</td>
<td>136,444</td>
<td>10,153</td>
<td>7,803</td>
<td>6,525</td>
<td>3,410</td>
</tr>
<tr>
<td>18-20</td>
<td>84,422</td>
<td>106,408</td>
<td>11,004</td>
<td>8,267</td>
<td>5,497</td>
<td>3,176</td>
</tr>
<tr>
<td>21-23</td>
<td>68,519</td>
<td>98,838</td>
<td>11,914</td>
<td>7,990</td>
<td>5,213</td>
<td>3,545</td>
</tr>
<tr>
<td>24-64</td>
<td>996,084</td>
<td>1,827,853</td>
<td>1,614,229</td>
<td>138,239</td>
<td>560,080</td>
<td>134,846</td>
</tr>
</tbody>
</table>

Percentage of the total population = Adolescents: Asthma > Depression > IBD > (psoriasis=JIA=T2D)

https://archive.pcornet.org/participating-networks/
How many adolescents with medical conditions are available for trials?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asthma Median, (Range)</th>
<th>Depression and Bipolar Disorder Median, Range</th>
<th>Type 2 Diabetes Median, Range</th>
<th>Inflammatory Bowel Disease Median, Range</th>
<th>Juvenile Idiopathic Arthritis Median, Range</th>
<th>Psoriasis Median, Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<td>Demographics</td>
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</tr>
</tbody>
</table>

Median number of adolescents per site:
Asthma > Depression >> (IBD=psoriasis=JIA=T2D)

https://archive.pcornet.org/participating-networks/
For combined studies, what indications might be feasible at pediatric hospitals?

### Top 20 Conditions Managed at US Children’s Hospitals (N=52) by Age – PHIS

#### Ages 12-17

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>8701</td>
<td>4.36258</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8238</td>
<td>4.13044</td>
</tr>
<tr>
<td>Major depressive disorders &amp; other/unspecified psychoses</td>
<td>6994</td>
<td>3.50671</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6901</td>
<td>3.46008</td>
</tr>
<tr>
<td>Depression except major depressive disorder</td>
<td>4739</td>
<td>2.37608</td>
</tr>
<tr>
<td>Other digestive system diagnoses</td>
<td>4109</td>
<td>2.06021</td>
</tr>
<tr>
<td>Asthma</td>
<td>4047</td>
<td>2.02912</td>
</tr>
<tr>
<td>Migraine &amp; other headaches</td>
<td>3696</td>
<td>1.85313</td>
</tr>
<tr>
<td>Sickle cell anemia crisis</td>
<td>3509</td>
<td>1.75937</td>
</tr>
<tr>
<td>Cellulitis &amp; other bacterial skin infections</td>
<td>2913</td>
<td>1.46055</td>
</tr>
<tr>
<td>Acute anxiety &amp; delirium states</td>
<td>2817</td>
<td>1.41241</td>
</tr>
<tr>
<td>Non-bacterial gastroenteritis w nausea &amp; vomiting</td>
<td>2703</td>
<td>1.35525</td>
</tr>
<tr>
<td>Bipolar disorders</td>
<td>2525</td>
<td>1.26601</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2274</td>
<td>1.14016</td>
</tr>
<tr>
<td>Other disorders of nervous system</td>
<td>2165</td>
<td>1.08551</td>
</tr>
<tr>
<td>Major hematologic/immunologic dx except sickle cell crisis &amp; coag</td>
<td>2020</td>
<td>1.01281</td>
</tr>
<tr>
<td>Infections of upper respiratory tract</td>
<td>1982</td>
<td>0.99375</td>
</tr>
<tr>
<td>Pneumonia NEC</td>
<td>1953</td>
<td>0.97921</td>
</tr>
<tr>
<td>Septicemia &amp; disseminated infections</td>
<td>1941</td>
<td>0.9732</td>
</tr>
<tr>
<td>Cystic fibrosis - pulmonary disease</td>
<td>1930</td>
<td>0.96768</td>
</tr>
</tbody>
</table>

#### Ages 18+

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>2335</td>
<td>4.13172</td>
</tr>
<tr>
<td>Seizure</td>
<td>2127</td>
<td>3.76367</td>
</tr>
<tr>
<td>Sickle cell anemia crisis</td>
<td>2116</td>
<td>3.7442</td>
</tr>
<tr>
<td>Cystic fibrosis – pulmonary disease</td>
<td>1411</td>
<td>2.49673</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1251</td>
<td>2.21361</td>
</tr>
<tr>
<td>Septicemia &amp; disseminated infections</td>
<td>1096</td>
<td>1.93934</td>
</tr>
<tr>
<td>Other digestive system diagnoses</td>
<td>916</td>
<td>1.62084</td>
</tr>
<tr>
<td>Migraine &amp; other headaches</td>
<td>779</td>
<td>1.37842</td>
</tr>
<tr>
<td>Non-bacterial gastroenteritis w nausea &amp; vomiting</td>
<td>725</td>
<td>1.28287</td>
</tr>
<tr>
<td>Cellulitis &amp; other bacterial skin infections</td>
<td>699</td>
<td>1.23686</td>
</tr>
<tr>
<td>Major hematologic/immunologic dx except sickle cell crisis &amp; coag</td>
<td>690</td>
<td>1.22094</td>
</tr>
<tr>
<td>Kidney &amp; urinary tract infections</td>
<td>673</td>
<td>1.19086</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>657</td>
<td>1.16254</td>
</tr>
<tr>
<td>Other disorders of nervous system</td>
<td>584</td>
<td>1.03337</td>
</tr>
<tr>
<td>Cardiac arrhythmia &amp; conduction disorders</td>
<td>574</td>
<td>1.01568</td>
</tr>
<tr>
<td>Chest pain</td>
<td>569</td>
<td>1.00683</td>
</tr>
<tr>
<td>Pneumonia NEC</td>
<td>558</td>
<td>0.98737</td>
</tr>
<tr>
<td>Other anemia &amp; disorders of blood &amp; blood-forming organs</td>
<td>549</td>
<td>0.97144</td>
</tr>
<tr>
<td>Infections of upper respiratory tract</td>
<td>458</td>
<td>0.81042</td>
</tr>
<tr>
<td>Asthma</td>
<td>444</td>
<td>0.78565</td>
</tr>
</tbody>
</table>

[https://www.childrenshospitals.org/phis](https://www.childrenshospitals.org/phis)
Summary

Preliminary analyses as of September 2019

ClinicalTrials.gov

• Approximately 60% of studies have been combined adult/child trials.
• Although there is variability in the use of combined trials, all but depression/bipolar disorder had >40% of their studies run as combined
• A large proportion of studies have used <12 and >12 years of age as their lower limit of inclusion.
  ✓ Notable exceptions: depression, IBD->16 years

PCORnet/PHIS

• For some conditions (IBD, JIA/RA, psoriasis, T2D), the number of adolescents per site is relatively low.
• Most of the top reasons for US hospital admissions (medically managed) are similar in 12-17 and 18+ years age groups
  ✓ Notable exceptions: psychiatric conditions-12-17 years; cardiac disorders-18+
Limitations

• **Clinicaltrials.gov**
  • Numerous age categories across studies makes defining lower ages of inclusion difficult
  • Heterogeneity of terms used in classifying studies may limit comparisons across time

• **PCORnet**
  • Inclusion and exclusion criteria are not captured, so the number of adolescent patients available for clinical trials is markedly less
  • Some referral pattern bias given PCORnet sites are larger medical centers

• **CHA-PHIS**
  • Admissions do not necessarily reflect the number of patients available
Scientific, Trial Design & Analytical Issues & Potential Solutions

Dionna Green, MD, FDA
Margaret Gamalo-Siebers, PhD, Eli Lilly
Defining the Population

What criteria should be used to determine suitable indications for adolescent-adult combined trials? What information is most useful in building a foundational understanding for an adolescent program (e.g., biomarker, pharmacodynamic [PD] response, safety)?

- Some considerations for the question:
  - Similarities between adult and adolescents in dose and PK parameters
  - Assumption of similarity of disease process (e.g., predictive biomarkers in disease path or defined surrogates) and expected similarity of drug effect
  - Is a young adult different physiologically from an adolescent in any way outside of age of majority? Why is this determination of importance (e.g., drug formulation, study endpoints)?
  - Lack of safety concerns in laboratory, animal and adult trials
  - Other factors such as severity of disease or unmet need, type of drug (e.g., NME vs new indication for an existing drug)

- Are certain diseases/therapeutic areas riskier? Does the decision tree on adolescent inclusion change based on the availability of data characterizing the safety profile for the class (e.g., is any unique set of adolescent data needed at all if safety is well characterized)?
What recommendations should be made in terms of:

- Dose selection (is PK information in adolescents available?)
- PK combined with adults or analyzed separately
- The number of adolescents required to complete a study in combined trials

What factors influence choice of design? What are the pros/cons of running an adolescent trial in parallel with an adult trial, especially for phase 3 trials, when it is not feasible or reasonable to include the adolescents in the adult trial?

- Borrowing/extrapolation of adult data for adolescent trials vs. adult-adolescent clinical trials. Is there any reason/need to perform sub-analyses of the adolescent population in an adult trial?
- Can data from adults be borrowed (Bayesian techniques) for the adolescent cohort so that a feasible number of adolescents can be enrolled in a timely fashion to assess efficacy? What special requirements would be needed for adaptive designs?

Do adolescent data from combined trials increase the ability to extrapolate in younger cohorts? What should criteria be for justification of extrapolation?

- What methods can be employed to better leverage adolescent data generated through inclusive early-phase research to inform younger pediatric cohorts?
Safety

Are there essential organ systems that should be assessed in adolescent subjects?

- How does an understanding of on-target effects of a candidate drug inform what organ systems require additional safety evaluation in adolescent subjects?

What are the scenarios that may require long-term safety studies in adolescent patients? What constitutes a long-term safety study for an adolescent?

- Recommendations for filing timeline and regulatory format changes
Bioethical Issues & Other Adolescent-Specific Factors

Donna Snyder, MD, FDA
Robert “Skip” Nelson, MD, PhD, J&J
Areas for Discussion

• Ethical considerations for enrolling adolescents into an adult trial
  • Principle of scientific necessity
  • Sufficient prospect of direct benefit to justify the risks
• The assumption of extrapolation
  • Necessary for enrolling adolescents into an adult trial?
  • Level of evidence?
• Timing of enrolling adolescents in an adult trial?
• Importance of previous experience with drug class?
• Approach to statistical analysis?
• Adult vs. adolescent outcome measures?
• Should enrollment in adult trials be limited to adolescents?
• Are there any unique issues for parental permission and adolescent assent when enrolling adolescents in an adult trial?
Panel Three

Operational Challenges, Lessons Learned & Proposed Solutions

Gregory Reaman, MD, FDA
Thomas F. Miller, PhD, Bayer
Areas for Discussion

- What are the critical elements for the optimal study site(s)?
- What is/are the objective(s) for enrolling adolescents on adult trials?
- Does off-label use of an approved drug impact enrolling adolescents on trials? Strategies to address?
- How best to incorporate the patient (adolescent) voice in study design and conduct?
- What are key strategies for recruitment? Incentives vs. inducement vs. coercion?
- What are the unique adolescent infrastructure requirements?
- How real are concerns that the same indication might differ between adolescents and adults? Are there design issues to address this?
- What are the roles for “wearables” or PADs for remote data entry?
- How can inclusion of adolescents on select trials satisfy Written Request requirements?