RA GDD, Regulatory & Development Policy
Pediatrics

Is it “feasible” to include adolescent populations in adult studies – and young adults in pediatric studies?

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Background

- Lack of adolescent trial inclusion in relevant adult trials may delay adolescent access to medicines
- Generally, adolescents are not eligible for enrollment in adult trials
- Historically, initial pediatric trials for medicines are initiated late in adult development, and/or often after a medicine has been approved
  - Slow adolescent accrual in pediatric trials, further delaying adolescent access to effective therapies

➢ To facilitate earlier access to investigational and approved drugs for adolescent patients, inclusion of adolescents in disease- and/or target-appropriate adult trials may be appropriate

Agenda

Is it “feasible” to include adolescent populations in adult studies – and young adults in pediatric studies?

- ✓ Yes, and No, and sometimes Maybe
- ✓ Initiatives
- ✓ Closing Thoughts

Yes, and No, and sometimes Maybe

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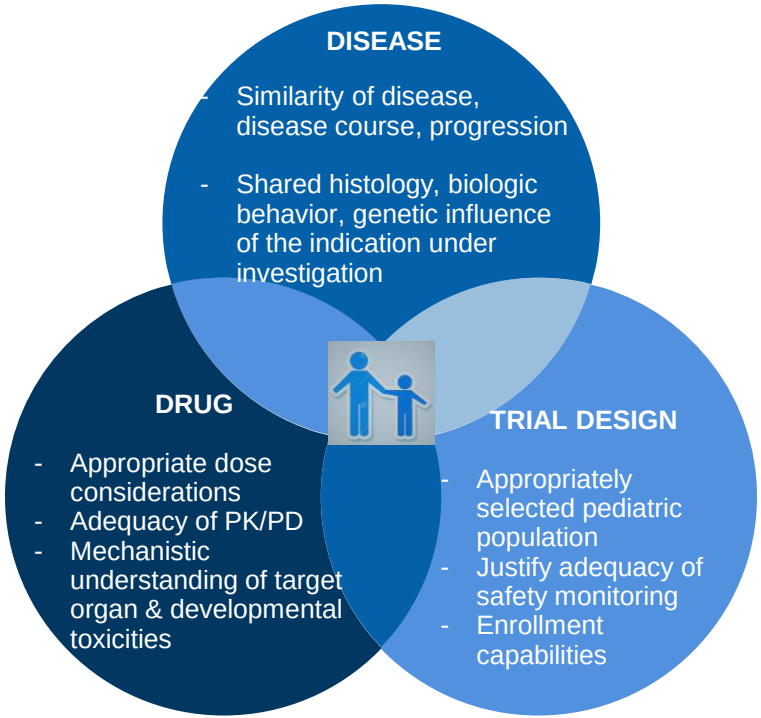
Ethical framework for pediatric research

Vulnerability of the research population

Children should only be enrolled in research if the scientific objective cannot be met through enrolling subjects who can consent personally	A suitable proxy for consent is required - Assent should be obtained	What is the potential benefit? Research risks to which children are exposed must be low	Children should not be placed at a disadvantage by being enrolled in a clinical trial - either through exposure to excessive risks, or - by failing to get necessary health care

Factors influencing "inclusive" research

Scientific factors

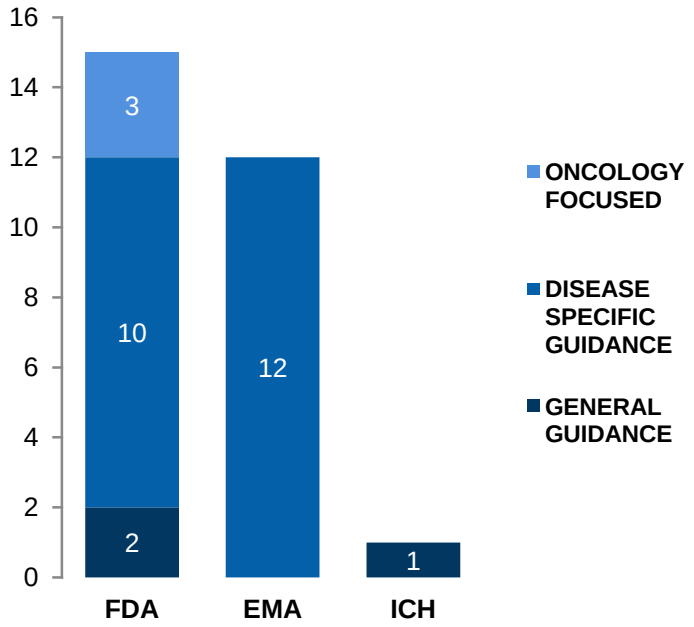


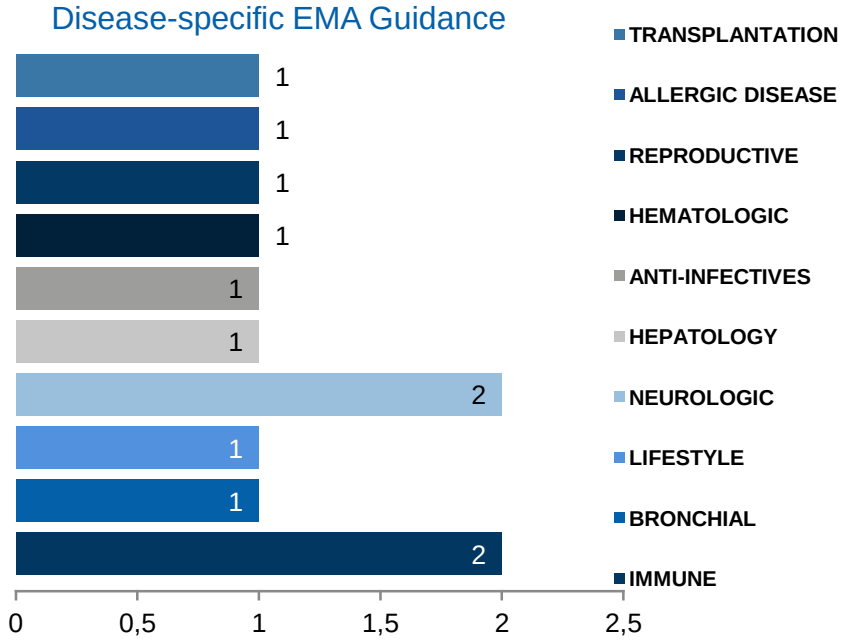
The inclusion of children in research is a complex and challenging issue

In addition to scientific justification:

- ✓ Compelling ethical justification
- ✓ The relevance of the study & its assessments for children with the disease
- ✓ Availability of therapeutic options

Existing regulatory guidance encouraging "inclusive" research





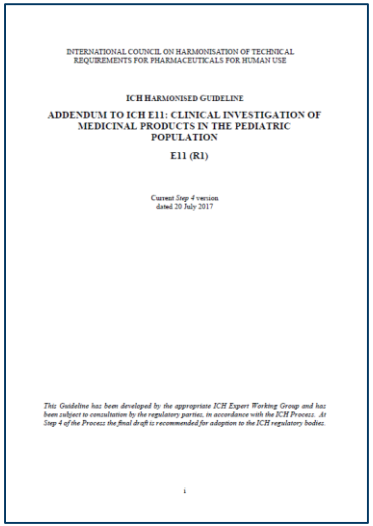
Regulatory Guidance

INTERNATIONAL COUNCIL ON HARMONISATION (ICH) OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

Clinical Investigation of Medicinal Products in the Pediatric Population: ICH E11 (R1) (July 2017)

https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf

"*Depending on factors such as the condition, the treatment, and the study design, it may be justifiable to include pediatric subpopulations in adult studies or adult subpopulations in pediatric studies..*"



INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Current Step 4 version
dated 20 July 2017

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the ICH regulatory bodies.

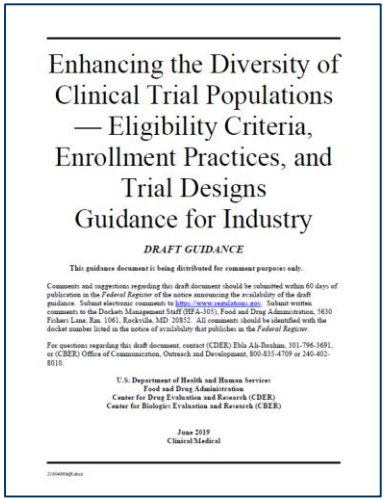
Regulatory Guidance

FDA DRAFT Guidance for Industry (June 2019)

Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

https://www.fda.gov/media/127712/download

"*Consider including children (ages 2 to 11 years) and adolescents (ages 12 to 17 years) in confirmatory clinical trials involving adults* ***when appropriate***."



Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Al-Ibrahim, 301-796-3691; or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2019
Clinical/Medical

What experience is there?

- Using *https://Clinicaltrials.gov* database
  - Site accessed 03 Oct 2019
- Filtered for
  - "*Child*" AND "*Adult*" studies
  - "*Completed*"
  - "*Studies with Results*"
  - "*Interventional Studies*"
  - "*Phase 1, 2, 3*" OR "*4*"
  - "*Industry*" sponsored
  - Funding type "*Industry*"
- 1,996 studies → 1,253 conditions

Top ‘Conditions’ using “inclusive” trial design

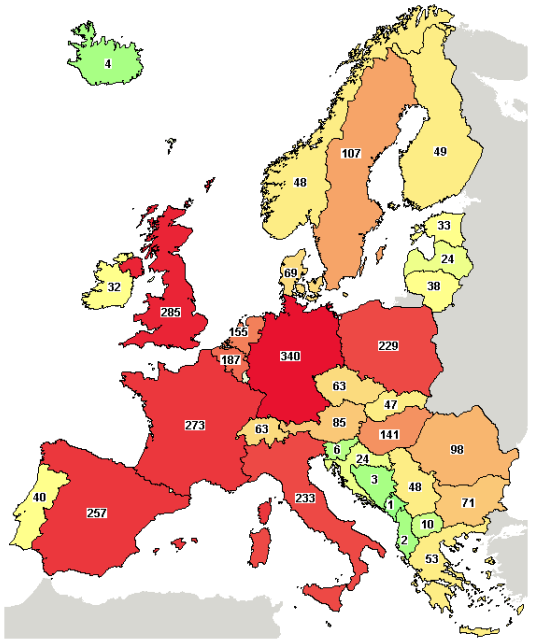
Communicable Diseases	Immune System Diseases	Respiratory Tract Infections	Genetic Diseases, Inborn	Hypersensitivity	Hypersensitivity, Immediate
541 STUDIES	**444 STUDIES**	**414 STUDIES**	**365 STUDIES**	**288 STUDIES**	**281 STUDIES**
Virus Diseases	Skin Diseases	Lung Diseases	Gastrointestinal Diseases	Digestive System Diseases	Central Nervous System Diseases
258 STUDIES	**245 STUDIES**	**234 STUDIES**	**217 STUDIES**	**217 STUDIES**	**206 STUDIES**
RNA Virus Infections	Respiratory Hypersensitivity	Respiratory Tract Infections	Syndrome	Metabolic Diseases	Brain Diseases
199 STUDIES	**196 STUDIES**	**190 STUDIES**	**189 STUDIES**	**175 STUDIES**	**173 STUDIES**
Hematologic Diseases	Neoplasms by Histologic Type	Neurologic Manifestations	Asthma	Lung Diseases, Obstructive	Bronchial Diseases
159 STUDIES	**150 STUDIES**	**132 STUDIES**	**131 STUDIES**	**125 STUDIES**	**124 STUDIES**

Source: ‘Conditions’ within search by https://clinicaltrials.gov (Site accessed 03 Oct 2019)

Nordic distribution of Interventional Studies with "inclusive" trial design

Nordic Country	# of studies	Nordic Country	# of studies
Denmark	69	Norway	48
Finland	49	Sweden	107
Iceland	4	* No inclusive studies reported in Greenland, the Faroe Islands, the Aland Islands, or Svalbard	

World = 1,996
Europe = 666



Source: European distribution of trial sites within search by https://clinicaltrials.gov

Example (1)

- ClinicalTrials.gov Identifier: *NCT00678886* GSK
- *Trial of Otelixizumab for Adults With Newly Diagnosed Type 1 Diabetes Mellitus (Autoimmune): DEFEND-1 (DEFEND-1)*
  - Purpose: to find out if an 8-day series of otelixizumab infusions leads to greater improvement in insulin secretion as compared with placebo infusion
  - Primary Outcome Measure: Change From Baseline in 2-hr Mixed Meal Stimulated C-peptide AUC (Normalized for 120-minute Time Interval) at Month 12
  - Subjects assigned to either otelixizumab or PBO 2:1 as an addition to insulin, diet, and other physician determined standard of care treatments
- Ages Eligible for Study: 12 Years to 45 Years
- Pediatric patients (n) = 29 completed the study

Example (2)

- ClinicalTrials.gov Identifier: *NCT00961441*

UCB Pharma

- *Study Evaluating the Pharmacokinetics of Keppra Extended Release (XR) in Children and Adults With Epilepsy*
  - Purpose: To study how the body absorbs, distributes, metabolises and eliminates Keppra XR in both children (12 to 16 years old) and adults (18 to 55 years old) with epilepsy
  - Primary Outcome Measure: Maximum Concentration at Steady State (Cmax) of Keppra XR Normalized by Dose and by Body Weight and Dose During up to 7 Days of Administration
  - Open-Label, Multicenter, Parallel-Group, Two-Arm Study
- Ages Eligible for Study: 12 Years to 55 Years
- Pediatric patients (n) = 12 patients < 16 years of age

Example (3)

- ClinicalTrials.gov Identifier: *NCT00560235*

Pfizer

- *Study Of CP-751,871 In Patients With Ewing's Sarcoma Family Of Tumors*
  - Purpose: Define the efficacy of CP-751,871 in patients with Ewing's sarcoma family of tumors
  - Primary Outcome Measure: Objective Response Rate (ORR) [Time Frame: Baseline and every cycle (4 weeks), for up to 6 cycles]
  - Non-randomized, Single group assignment, Open-label
- Ages Eligible for Study: 10 Years and older
- Pediatric patients (n) = 78 patients < 18 years of age

Facilitating inclusive research (1)

Tools and knowledge to inform program development

Translational animal models

To effectively predict human drug doses that are applicable to pediatric populations

- Understanding of species differences to enhance knowledge of age specific maturation in different organ systems

Child-friendly formulations

To ensure accurate, acceptable, and palatable doses

- Bioequivalence studies should start much earlier in the drug development process
- Knowledge of how manipulation of the adult formulation affects the PK

Modeling techniques

To improve the design and conduct of clinical studies in pediatric patients and drug development efficiency

- PopPK modeling reduces the need for large blood volumes and invasiveness

Foundational knowledge of disease

To improve selection of patient population and appropriate end-points / biomarkers

- Characterization of disease spectrum and severity; Role for and sensitivity of diagnostic testing to better inform trial design and assumptions

Facilitating inclusive research (2)

Choice of Control Group

Placebo Control

Consider:

- Using “add on” to existing standard of care (or efficacious treatment)

Active Treatment Control

Consider:

- Non-inferiority design (leveraging previous data from PBO-controlled trials to estimate the non-inferiority margin)

External Controls

Consider:

- Leveraging natural history data to minimize impact to new patient size

Alternative Design

Consider:

- Dose-response designs with more than 1 dose
- Avoids use of PBO

Initiatives

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EFGCP Position Statement: Age inclusive research

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.

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ACCELERATE Platform: FAIR Trials Working Group

Fostering Age Inclusive Research

FAIR Toolkit

- Regulatory Guidance
- eCRF and Standard Analyses
- Patient Reported Outcomes (PROs)
- Assent templates for adolescents
- Protocol Elements
- Examples of HA/EC considerations on AYA
- List of AYA-clinical sites
- List of approved protocols including adolescents in adult trials

FAIR for AYA Stamp

https://www.accelerate-platform.org/work-programme/ongoing/why-fair-trials/

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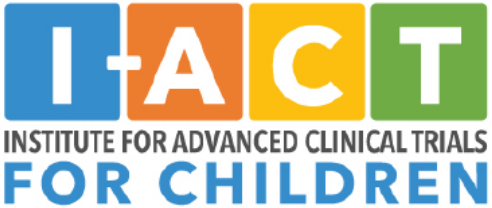
Conect4children Consortium: Collaborative European network

- Work Package 4: Scientific advice, feasibility, and innovation
  - ✓ *Aims to create the processes to provide the network's clients with advice on several aspects of paediatric drug development, including experts' opinions on particular diseases and study design, patients/parents representative groups which will ensure the patient-centred approach in the advice given, and innovative methodology experts to assist in developing new ways to overcome the hurdles of children's drug development*
- Work Package 7: Planning and execution of clinical trials
  - ✓ *Works in close connection with Work Package 2 (Organization and governance of the pan-EU paediatric clinical trials network), implementing processes and tools created by that work package, testing them in the proof-of-viability trials, and refining them based on their experiences before the end of the c4c project*

iACT for Children: Pediatric Research Innovation Forum

Inclusion of Adolescents in Adult Clinical Trials



- Workshop 15 & 16 October
- Focus on bioethical, scientific, and operational issues related to inclusion of adolescents in adult clinical trials that are designed to assess the efficacy and safety of investigational drugs
- Goal: To define the major gaps and develop recommendations to support implementation

Closing Thoughts

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We have an opportunity to facilitate meaningful change in how we develop medicines for adolescents

Leveraging knowledge about disease and drug, and maximizing trial design, may create an opportunity for **inclusive** approaches to adolescent medicines development

Successful transformational change requires forward-thinking strategy and regulatory alignment

The children are depending on us

There can be no keener revelation of a society's soul than the way in which it treats its children.

— Nelson Mandela, Former President of South Africa-

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Thank you

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