Integration of Paediatric Development into Drug Development – How and When to Include Adolescents in Adult Research

4th Nordic Paediatric conference
Helsinki, 14 September 2022

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On behalf of the EFGCP Children’s Medicines Working Party ‘Adolescent Inclusion in Adult Trials’ study team
• European Forum for Good Clinical Practice (EFGCP) is a not-for-profit organization established by, and for, those with interest in the development of medicines and medical technologies

• EFGCP’s Children’s Medicines Working Party (CMWP) is a multi-stakeholder workgroup focused on contributing to ethical, scientific, legal, safety and societal issues related to the design, conduct, analysis and reporting of biomedical research and development of new medicines for children of all ages
Problem Statement

• The average time between approval and labelling of a new medicine for adults and children is nearly a decade*

• Adolescent trials are typically not initiated until after the benefit-risk for a new medicine has been established in adults (either late in adult medicines development or after approval)
  
  • Off-label availability of adult medicines contributes to slow adolescent accrual in pediatric investigational trials, further delaying access to effective therapies
  
  • Delays in evaluation of potential treatments for children who presented with MIS-C during the SARS-CoV-2 pandemic has heightened awareness of this disparity**

• Inclusion of adolescents in disease- and/or target-appropriate adult trials may facilitate earlier adolescent access to effective therapies

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EFGCP CMWP convened a roundtable discussion (Oct 2018) with regional stakeholders to identify opportunities and actions promoting age-inclusive research.

- **Objective:** To share perspectives and identify areas of mutual research interest
- **Conducted:** (1) environmental analysis of the current ‘State of Play’, (2) SWOT analysis, (3) Gap analysis
- **SWOT & Gap analysis identified a need to define trial attributes that may facilitate age-inclusive trial design**

**Adolescent Inclusion Position Statement**
- **Feb 2019**
- **Endorsed by EFGCP Board**

**Global multistakeholder working groups**
- **Mar 2019**
- **WG 1: Role of adolescent inclusion in regulatory decision-making**
- **WG 2: Defining prerequisites for adolescent inclusion in adult trials**

**Research & Publication**
- **Deliverables:**
  - Review regulatory guidance (Completed; Manuscript submitted for peer review)
  - Development of adolescent definition for use in regulatory decision making (Completed)
  - Development of ‘Adolescent Inclusion Decision Tree’ (beta-testing Completed)

**Output of 2018 roundtable**

EFGCP = European Forum for Good Clinical Practice; CMWP = Children’s Medicines Working Party
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Project Background & Aim

• Due to perceived vulnerability, pediatric trials are often delayed until after a medicine has demonstrated a positive benefit-risk in adults

• Pediatric clinical studies agreed to be completed after marketing authorization in adults have been associated with a lower likelihood of eventual completion\(^1,2\)
  • Factors include (not limited to) availability of off-label medications, trial complexity, infeasible sample size, lack of adequate research infrastructure

• When appropriate, enrolment of adolescents into certain adult clinical trials may expedite adolescent access to therapies

• **Project Aim:** Development of a tool for use by trial sponsors, investigators, IRBs, regulators to facilitate alignment on age-inclusive trial designs

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\(^1\) Hwang TJ, Tomasi PA, Bourgeois FT. Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study. PLOS journals 2018. 15(3): e1002520.

Qualitatively Analyzed “Adolescent/-ce” Definitions In Jurisdictions Commonly Participating In Pediatric Medicines Research

Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products; Proposed Rule (21 CFR Parts 201, 312, 314, and 601); 20 CFR 416.924a – ‘Age as a factor of evaluation in childhood disability’; Section 520(m)(6)(E)(i) of the FD&C Act; 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); Guideline on good pharmacovigilance practices (GVP) – P. IV EMA/572054/2016; [link]

http://www.hra-decisiontools.org.uk/consent/principles-children-EngWalesNI.html; The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031) Article 2; Established under Swiss Civil Code in 1907 [link], Federal Act on Research involving Human Beings (Human Research Act, HRA) With the authority of the Federal Assembly of the Swiss Confederation (on the basis of Article 118b paragraph 1 of the Federal Constitution; Age Limits and adolescence. Paediatric Child Health. 2003 Nov; 8(9): 577; The Ministry of Foreign Affairs of Japan - II. ARTICLE 1 (Definition of the child) B. Age limitation applied to legal competency in Japan; The Minors Protection Law, art. 2; ICH E11 (2000); WHO website [link].
Three Common Themes Were Identified In Regional Adolescent Definitions

- **Age of Majority**: Age as an objective measure for use in legal proceedings, establishing legal rights and/or as part of sentencing processes.

- **Developmental/Physiological**: Reflects the physical/physiologic aspects of maturation.

- **Behavioral**: Reflects the rapid development of the brain during adolescence, in particular the later acquisition of more mature processing (planning and impulse control).
Across regional regulatory jurisdictions, adolescence is typically defined utilizing chronological age, often reflecting the legal age of majority in that region. These definitions roughly correspond with the period of time between the ages of 10 and 20 years of life.

However, adolescence is a period of development characterized by sexual maturation (puberty), a variable and accelerated rate of growth and continued neurocognitive development.

Some therapies and some illnesses may delay or accelerate the onset of puberty and can have an effect on the pubertal growth spurt. By altering the pattern of growth, they may affect final adult height. Similarly, some therapies and some illnesses may have an impact on evolving cognitive or emotional changes or be influenced by the hormonal changes around puberty.

These developmental, therapeutic and disease-related considerations may therefore broaden the adolescent age range beyond those ages associated with the regional or legal definition of ‘adolescent’.
The aim of the tool is to define key considerations fostering adolescent inclusion in appropriate trials (for use by trial sponsors, investigators, health agencies, and ethics committee members)
Seven Factors Gating/Enabling Adolescent Inclusion Were Identified

*Identified as part of Horizon Scanning activity
The Adolescent Inclusion Decision Tree

Overarching Themes

At every stage of the process of designing clinical development programs for investigational medicinal products in adults, the inclusion of adolescents in the clinical trial program should be considered. For purposes of this decision tree, we have used the International Conference on Harmonisation (ICH) definition to establish the upper age cut-off for the adolescents.

Inclusion of adolescents within an investigational program not only facilitates the generation of data for the use in determination of beneficence in the adolescent population, it can also serve as a meaningful pathway to facilitate earlier access for adolescents to effective therapies, and enhance commercial access strategies nationally. Additionally, the inclusion of adolescents in adult trials may facilitate earlier generation of data relevant to the design of studies for younger age pediatric settings (children, toddlers, infants, neonates).

Now adolescents are included within trial designs, should take into consideration how the data generated in the trial is to be used to answer questions specific to the adolescent population with the indication of study, or as a means to facilitate evaluation of younger age cohorts within the pediatric development program, or both. As new data is generated, the opportunity for adolescent inclusion should be continuously reassessed.

A set of overarching generalities should be kept in mind when adolescent inclusion is considered for a development program or trial design, as follows:

1. Individual biases or sensitivities of sponsor/investigational committee members should not support the omission of the adolescent population being asked to participate in the trial. Adolescent input should be sought by sponsor/investigational committee members during the study design phase and the ethics review.

2. Perceived vulnerability should not be a barrier to research. Studies should not be refused to the adolescent population just because they are perceived to be difficult due to ethical methodology, as well as operational specifics. Meaningful partnerships should be developed between the sponsor, the adolescent population, and appropriately experienced regulators, researchers, and clinical care staff to develop trial that are inclusive and take into account the needs of the participants.

3. When adolescent inclusion is considered, it may be important to institutionalize (modify) protocols to facilitate adolescent inclusion, even if the initial assessment for the adolescent inclusion in adult trials using the criteria below is considered and determined to be inappropriate. Exploring alternative study designs may better accommodate the requirements for data generation across the adolescent and adult populations.

4. Inclusion of adolescents within adult research programs may also facilitate a broader population for consideration in explorations regarding health technology assessments (HTAs) or formulary decisions, or in establishing national pricing.

Finally, when young adults (aged 19 – 25 years) have been included in early phase research, they may serve as a rich and valuable data source to inform on the appropriateness of adolescent concerns as clinical trial participants within the confirmatory development program or offer earlier phase trials. Across regulatory jurisdictions, there is no widely accepted regulatory definition of young adult. Therefore, we consider the ICH upper age cut-off for adolescents as the starting age for young adults, correlating roughly to the ages of 18 up to 30 years of age.
The Adolescent Inclusion Decision Tree

- Provides users with a set of over-arching principles for consideration when adolescent inclusion may be relevant to a medicine development program or trial design.
The Adolescent Inclusion Decision Tree

- Each of the seven factors is incorporated
- A brief background discussion highlights each factor’s relevance
The Adolescent Inclusion Decision Tree

- Each of the seven factors is incorporated
- A brief **background discussion** highlights each factor’s relevance
- A **list of key questions** to be addressed (by sponsors, investigators, IRBs, regulators) when considering adolescent inclusion
Example of Key Questions

Disease Considerations

4. Are there similar diagnostic methods and/or available therapeutic management options for adolescents and adults with the disease?

5. Are there clinically meaningful outcomes for assessment in adolescents that align with outcomes assessed in the adult population? Are there comparable trial endpoints applicable to adolescents and adults with disease?
Beta-testing Conducted to Refine Tool’s Functionality and Usability

- Invitations sent to targeted end users in the EU & US
- Opened 03 Jan 2022 – Closed 15 Mar 2022

Focus areas for testing were:
1. **Functionality** *(how “useful” is the tool in your role?)*
2. **Interpretability** *(how “understandable” is each component of the tool?)*
3. **Usability** *(how “easy” is the tool to use?)*
4. Identification of **gaps** *(defined for purposes of testing as “critical errors of omission”)*
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Testing packets included
1-page Welcome correspondence
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1-page Testing Instructions
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Testing packets included
Testing Log (pre-defined VAS scoring, pre-defined to evaluate each ‘Focus Area’)

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**Testing Log**

**Focus Area:** Functionality

- **Tool expertise:**
  - User experience
  - Tool functionality
  - Health policy

**VAS Scoring:** (0-10)

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<thead>
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<th>Area</th>
<th>Score</th>
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<tbody>
<tr>
<td>Functionality</td>
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**Focus Area:** Interpretability

- **Understanding:**
  - Component clarity

**VAS Scoring:** (0-10)

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<thead>
<tr>
<th>Area</th>
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Decision Tree
Beta-testing Findings

• 6 testers returned completed Logs
  o Overall **Functionality** of the tool rated high (VAS range = 5 [Excellent] – 4 [Very Good])
  o **Interpretability** of each Factor
    • Operational, Investigator & Site Focused, and Sponsor Focused topics and their Key Questions rated high (VAS range 5 [Excellent] – 4 [Very Good])
    • Disease, Product, Statistical, and Legal & Ethical topics each had individual Key Questions that rated low
      • Low scoring Key Questions were consistent across testers
      • In free text comments, testers recommended simplification of text to resolve low scores (specifically to benefit non-native English speakers)
  o Overall **Usability** of the tool rated high (VAS range = 5 [Excellent] – 4 [Very Good]) with the exception of one tester (VAS range 3 [Good])
  o No **gaps** identified
  o One tester suggested that functionality of the tool may be improved with addition of a formal scoring schema
Summary & Next Steps

• To our knowledge, this is the first comprehensive tool designed to foster structured consideration of adolescent inclusion in adult trials

• Including adolescents in adult clinical trials will play an important role in facilitating their timelier access to new medicines

• Challenges exist in involving adolescents in trials before the safety and efficacy of new medicines are established for adults

• This tool has been developed incorporating scientifically and ethically sound principles to facilitate adolescent inclusion in the design and execution of relevant adult trials

➢ Next Steps include

• Refinement of the tool leveraging beta-testing findings
• Socialization of tool in relevant research communities
• Publication of tool & development methodology
• Launch of the tool on 19 October 2022
Christina Bucci-Rechtweg, Novartis Pharmaceuticals Corporation (East Hanover, NJ, US)
Kristina An Haack Bonnet, Sanofi S.A. (Paris, Ile de France, France)
Martin Edwards, Noah’s Ark Children’s Hospital for Wales (Cardiff, Wales, UK)
Menia Koukougianni, Patient Advocate, NGO Karkinaki (Greece)
Martine Dehlinger Kremer, ICON Plc (Wiesbaden, Hesse, Germany)
Margaret Gamalo, Pfizer (Collegeville, PA, US)
Ensio Norjavaara, Astra Zeneca (Gothenburg, Sweden)
Rhian Thomas Turner, Noah’s Ark Children’s Hospital for Wales (Cardiff, Wales, UK)

Acknowledgments
Bryan Michaux (EFCGP), Odile Chantrenne (EFGCP), Ingrid Klingmann (EFGCP), the EFGCP Children’s Medicines Working Party
Thank You for your Attention

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