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

EFGCP & CMWP

- 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

*Carmack M, Hwang T, Bourgeois FT. Pediatric Drug Policies Supporting Safe and Effective Use of Therapeutics in Children: A Systematic Analysis. Health Aff (Millwood) 2020; 39(10): 1799-1805;
**Hwang T, Randolph A & Bourgeois F. Inclusion of children in clinical trials of treatments for coronavirus disease 2019 (COVID-19). JAMA Pediatr. 2020. 174:825–826.

Project Background

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*

Output of 2018 roundtable

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 pre-requisites 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)

EFGCP = European Forum for Good Clinical Practice; CMWP = Children's Medicines Working Party

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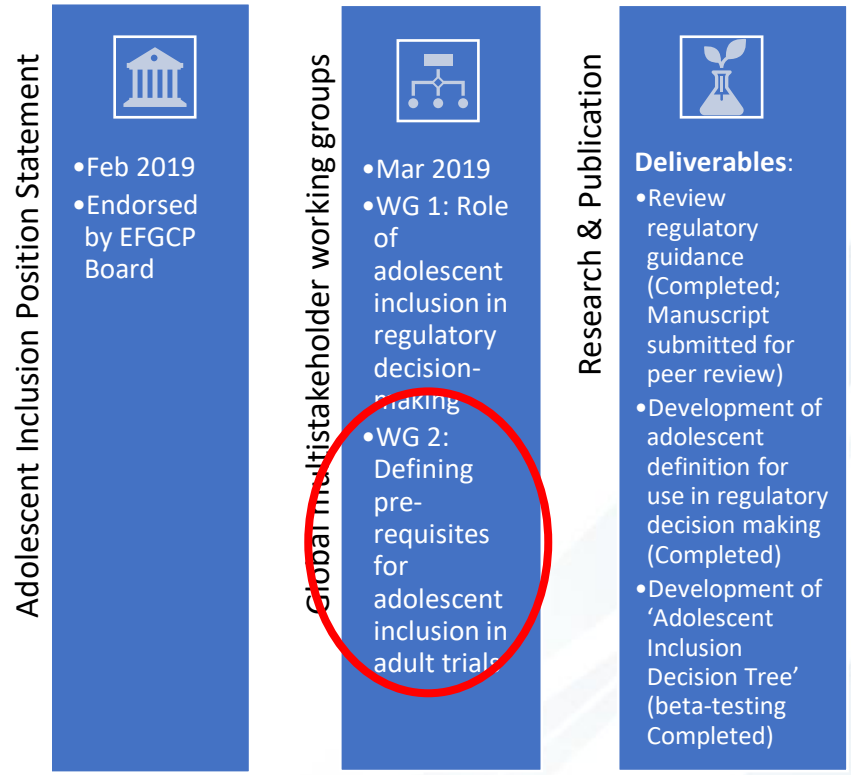

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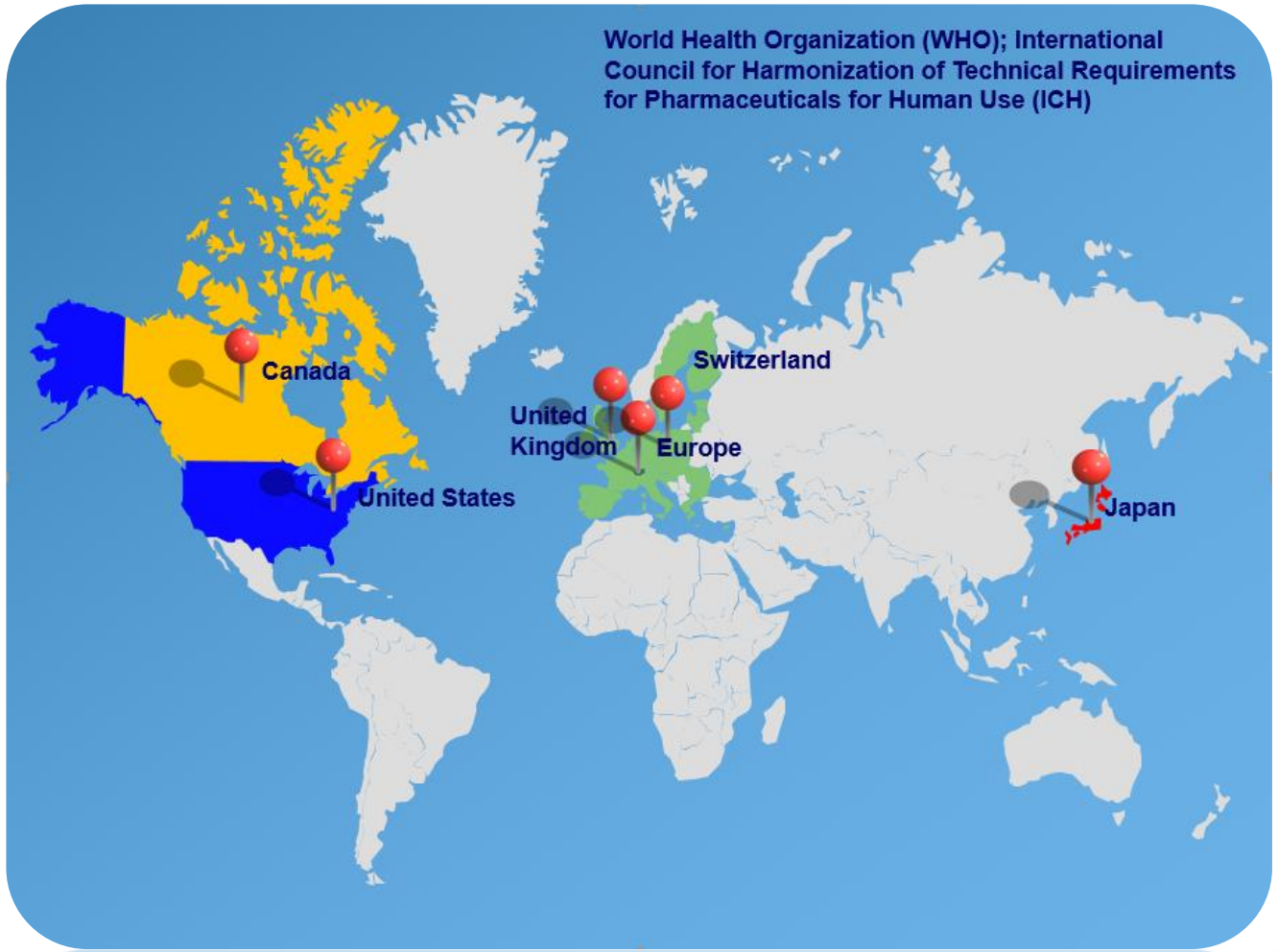
Project Background & Aim

- 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

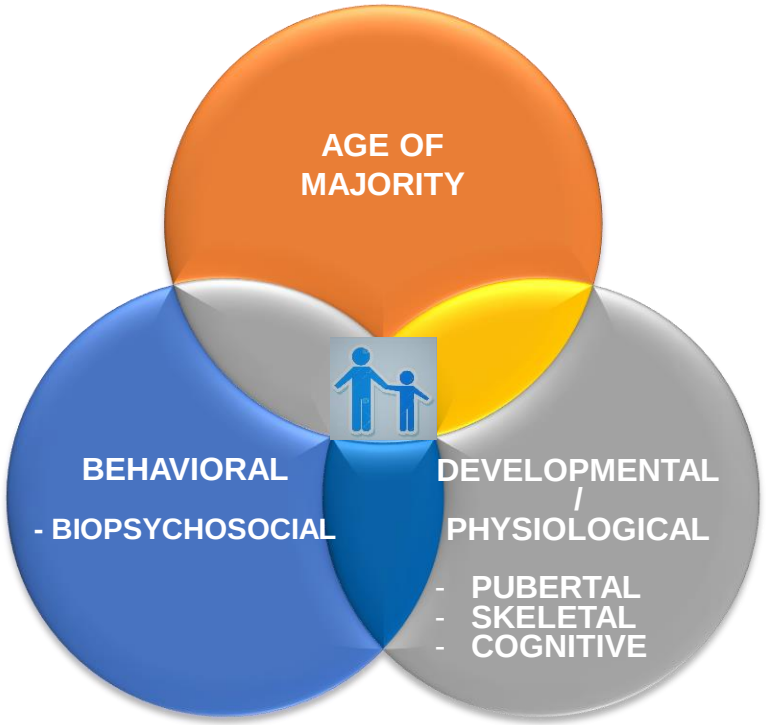
[1]Hwang TJ, Tomasi PA, Bourgeois FT. Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study. PLOS journals 2018. 15(3): e1002520.; [2]Hwang TJ, Orenstein L, Kesselheim AS, Bourgeois FT. Completion Rate and Reporting of Mandatory Pediatric Postmarketing Studies Under the US Pediatric Research Equity Act. JAMA Pediatr 2019. 173(1): 68-74.

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; 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 https://www.youthpolicy.org/wp-content/uploads/library/Switzerland_1907_Civil_Code_eng.pdf ; 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 https://apps.who.int/adolescent/second-decade/section2/page1/recognizing-adolescence.html.

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)

Study Team Leveraged Common Themes To Develop A Holistic Definition of "Adolescent/-ce" For The Project

PROJECT DEFINITION

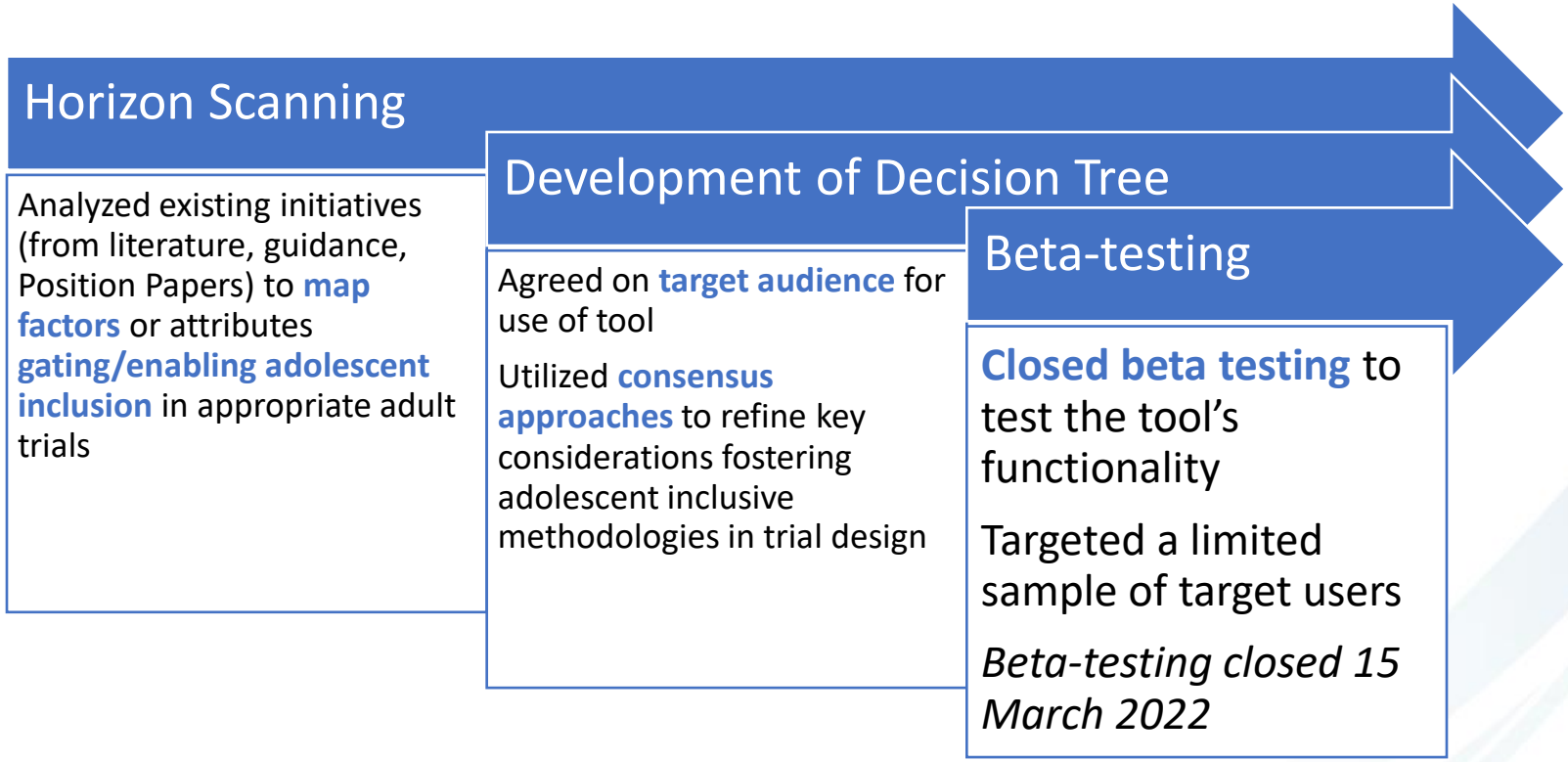
Across regional regulatory jurisdictions, **adolescence is typically defined utilizing chronological age**, often reflecting the legal age of majority in that region. These definitions roughly correspond with the period of time between the ages of 10 and 20 years of life.

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'.

Three Phases In Development Of The Adolescent Inclusion Decision-Tree



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

- Disease
- Product
- Statistical
- Operational
- Investigator & Site-focused
- Sponsor-focused
- Legal & Ethical

*Identified as part of Horizon Scanning activity

The Adolescent Inclusion Decision Tree

Over-arching themes

At every step 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 adolescents (https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf). Inclusion of adolescents within an investigational program not only facilitates the generation of data for use in determination of benefit-risk in the adolescent population, it can also serve as a meaningful pathway to facilitate earlier access for adolescents to efficacious 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 cohorts (children, toddlers, infants, neonates).

How 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 over-arching generalities should be kept in mind when adolescent inclusion is considered for a development program or trial design, as follows:

1. Individual biases or opinions of sponsors/investigators/ethics committee members should not supplant the opinions of the adolescent population being asked to participate in the trial. Adolescent input should be sought by sponsors/regulators/ethics committee members during the study design phase and its ethics review.
2. Perceived vulnerability should not be a barrier to research. Studies should not be refused in the adolescent population just because they are perceived to be difficult due to ethical, methodological, as well as operational specificities. Meaningful partnerships should be developed between the sponsor, the adolescent population and appropriately experienced regulators, research and clinical care staff to develop trials that are inclusive and take into account the needs of the participants.
3. When adolescent inclusion is considered, it may be important to individualize (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 program may also facilitate a broader population for consideration in negotiations regarding Health Technology Assessments (HTAs) or formulary decisions, or in establishing national pricing.

Finally, when 'young adults' (aged 19 – 30 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 cohorts as clinical trial participants within the confirmatory development program or other 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 19 up to 30 years of age.

2

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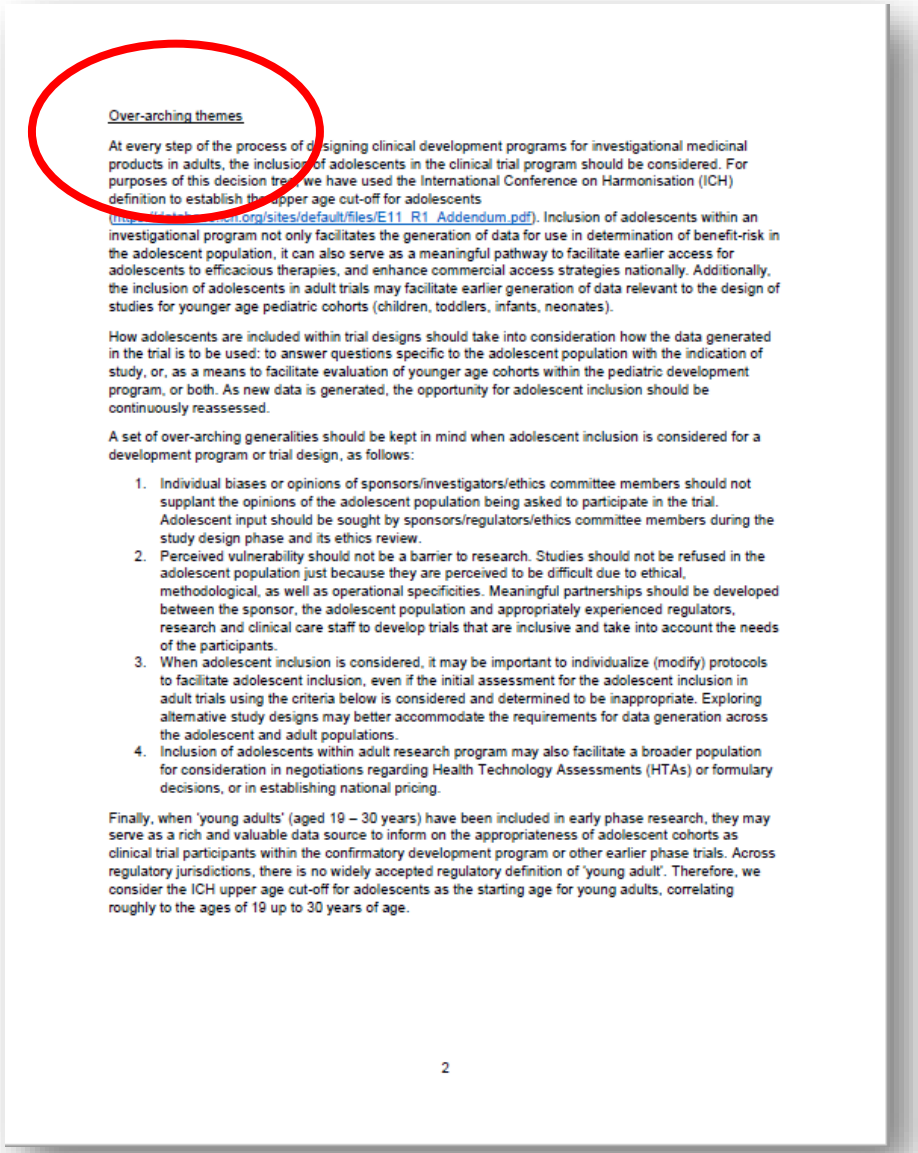

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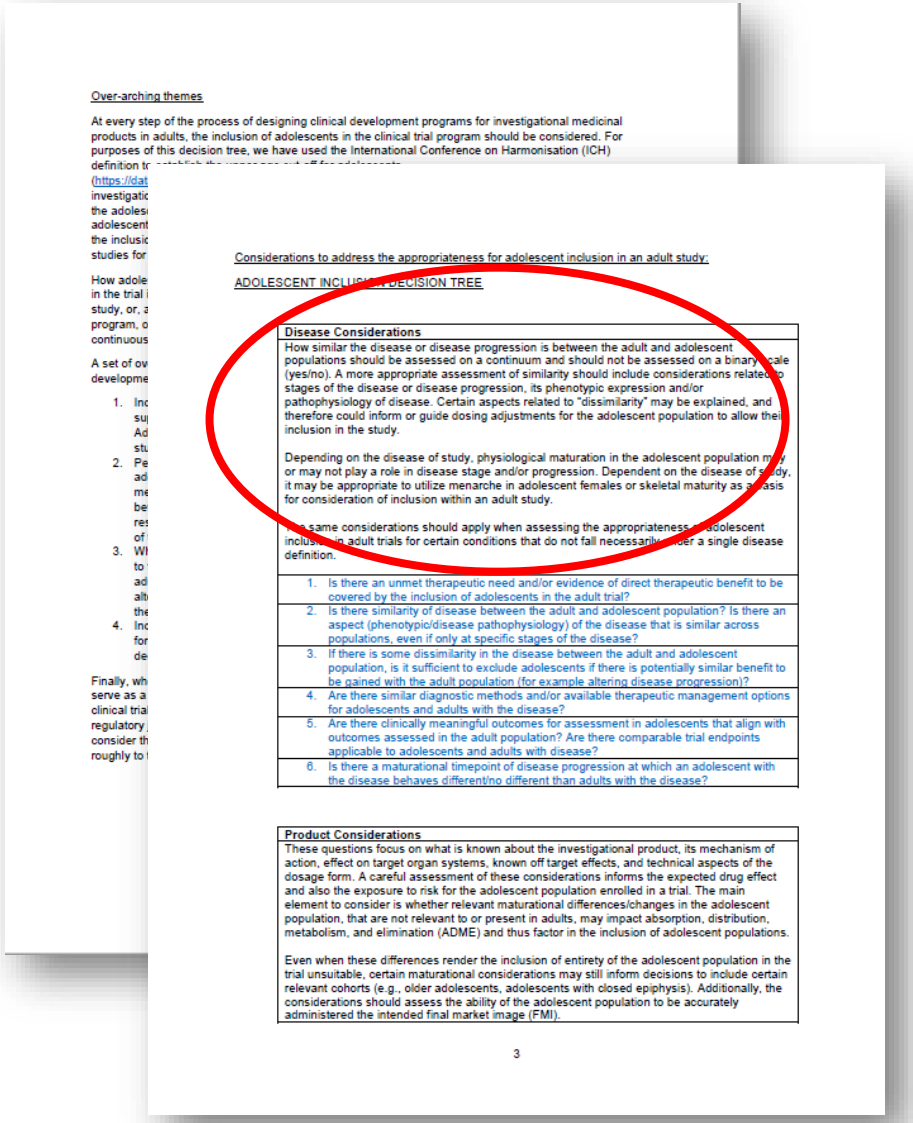
2

- 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



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Considerations to address the appropriateness for adolescent inclusion in an adult study:

ADOLESCENT INCLUSION DECISION TREE

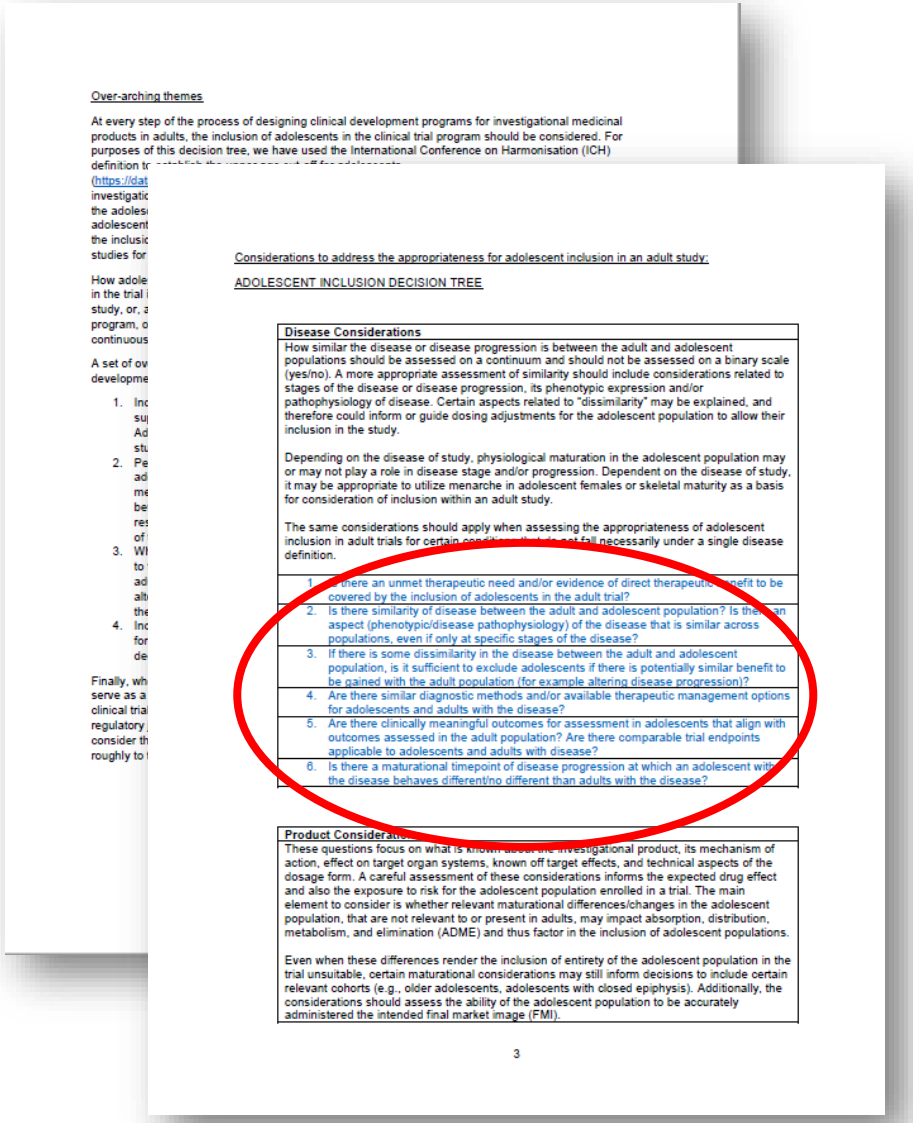
Disease Considerations
How similar the disease or disease progression is between the adult and adolescent populations should be assessed on a continuum and should not be assessed on a binary scale (yes/no). A more appropriate assessment of similarity should include considerations related to stages of the disease or disease progression, its phenotypic expression and/or pathophysiology of disease. Certain aspects related to "dissimilarity" may be explained, and therefore could inform or guide dosing adjustments for the adolescent population to allow their inclusion in the study. Depending on the disease of study, physiological maturation in the adolescent population may or may not play a role in disease stage and/or progression. Dependent on the disease of study, it may be appropriate to utilize menarche in adolescent females or skeletal maturity as a basis for consideration of inclusion within an adult study. The same considerations should apply when assessing the appropriateness of adolescent inclusion in adult trials for certain conditions that do not fall necessarily under a single disease definition.
1. Is there an unmet therapeutic need and/or evidence of direct therapeutic benefit to be covered by the inclusion of adolescents in the adult trial?
2. Is there similarity of disease between the adult and adolescent population? Is there an aspect (phenotypic/disease pathophysiology) of the disease that is similar across populations, even if only at specific stages of the disease?
3. If there is some dissimilarity in the disease between the adult and adolescent population, is it sufficient to exclude adolescents if there is potentially similar benefit to be gained with the adult population (for example altering disease progression)?
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?
6. Is there a maturational timepoint of disease progression at which an adolescent with the disease behaves different/no different than adults with the disease?

Product Considerations
These questions focus on what is known about the investigational product, its mechanism of action, effect on target organ systems, known off target effects, and technical aspects of the dosage form. A careful assessment of these considerations informs the expected drug effect and also the exposure to risk for the adolescent population enrolled in a trial. The main element to consider is whether relevant maturational differences/changes in the adolescent population, that are not relevant to or present in adults, may impact absorption, distribution, metabolism, and elimination (ADME) and thus factor in the inclusion of adolescent populations. Even when these differences render the inclusion of entirety of the adolescent population in the trial unsuitable, certain maturational considerations may still inform decisions to include certain relevant cohorts (e.g., older adolescents, adolescents with closed epiphysis). Additionally, the considerations should assess the ability of the adolescent population to be accurately administered the intended final market image (FMI).

3

- Each of the seven factors is incorporated
- A brief **background discussion** highlights each factor's relevance

The Adolescent Inclusion Decision Tree



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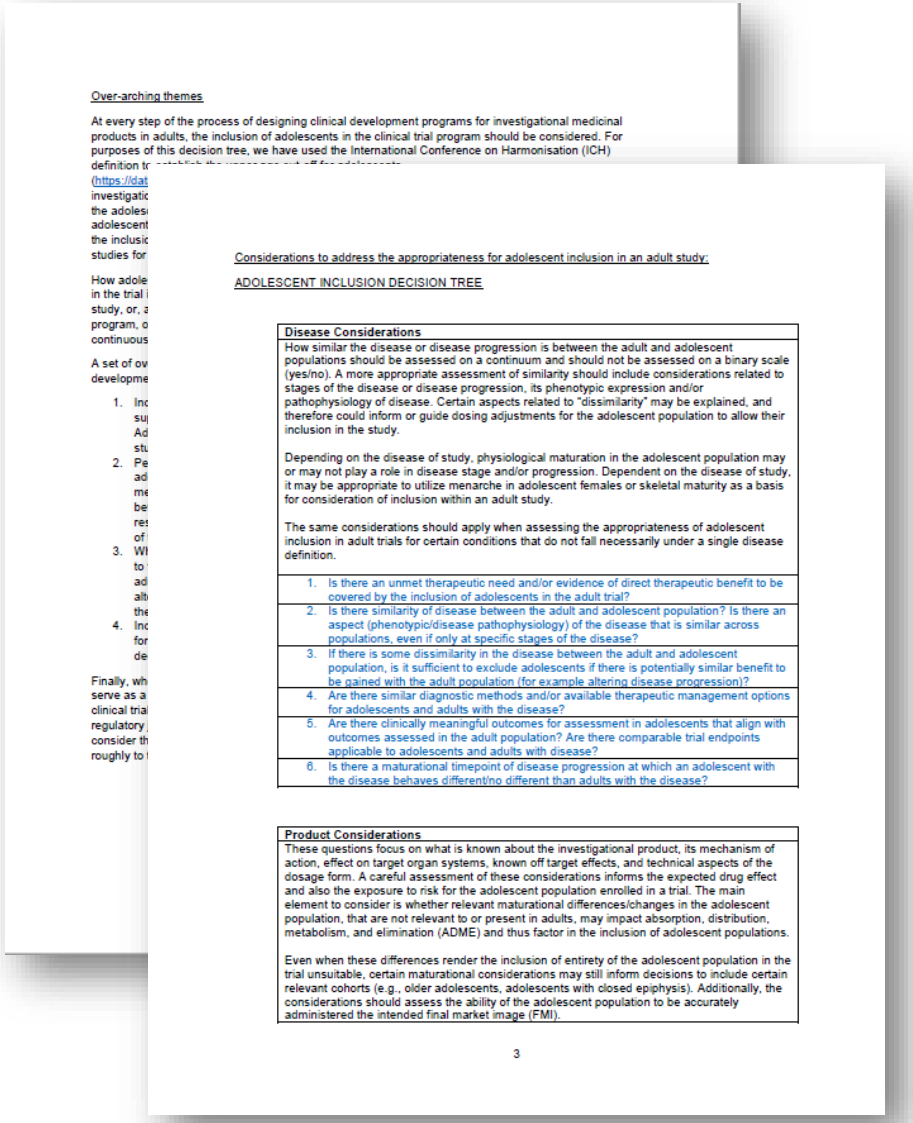
- Each of the seven factors is incorporated
- A brief **background discussion** highlights each factor's relevance
- A **list of key questions** to be addressed (by sponsors, investigators, IRBs, regulators) when considering adolescent inclusion

Example of Key Questions



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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")*

Testing packets included

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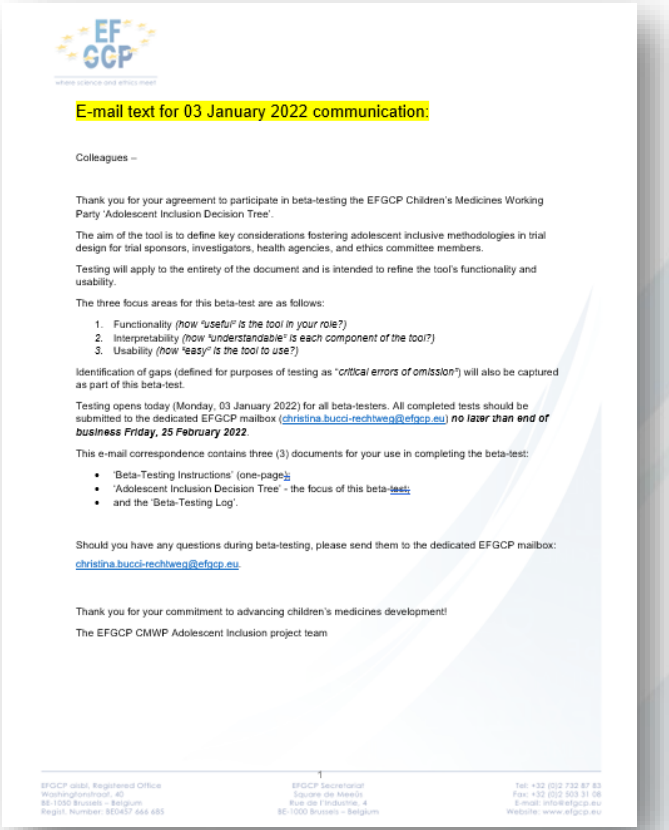
Testing packets included

1-page Welcome correspondence



E-mail text for 03 January 2022 communication:

Colleagues –

Thank you for your agreement to participate in beta-testing the EFGCP Children's Medicines Working Party 'Adolescent Inclusion Decision Tree'.

The aim of the tool is to define key considerations fostering adolescent inclusive methodologies in trial design for trial sponsors, investigators, health agencies, and ethics committee members.

Testing will apply to the entirety of the document and is intended to refine the tool's functionality and usability.

The three focus areas for this beta-test are as follows:

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?)*

Identification of gaps (defined for purposes of testing as "*critical errors of omission*") will also be captured as part of this beta-test.

Testing opens today (Monday, 03 January 2022) for all beta-testers. All completed tests should be submitted to the dedicated EFGCP mailbox (christina.bucci-rechtweg@efgcp.eu) ***no later than end of business Friday, 25 February 2022***.

This e-mail correspondence contains three (3) documents for your use in completing the beta-test:

- 'Beta-Testing Instructions' (one-page);
- 'Adolescent Inclusion Decision Tree' - the focus of this beta-test;
- and the 'Beta-Testing Log'.

Should you have any questions during beta-testing, please send them to the dedicated EFGCP mailbox: christina.bucci-rechtweg@efgcp.eu.

Thank you for your commitment to advancing children's medicines development!

The EFGCP CMWP Adolescent Inclusion project team

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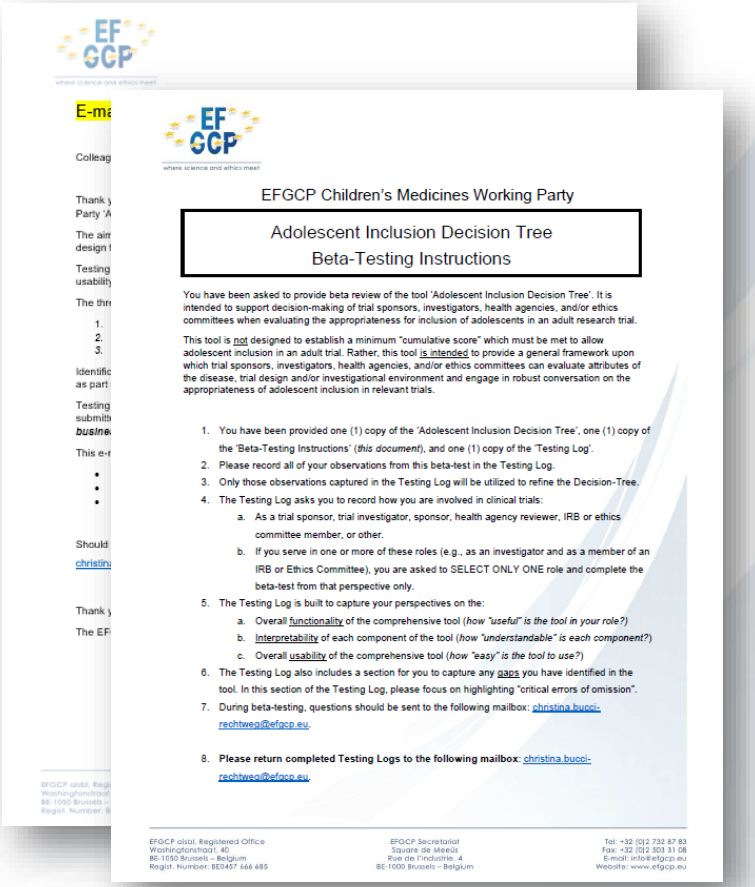
1-page Testing Instructions



EFGCP Children's Medicines Working Party

Adolescent Inclusion Decision Tree
Beta-Testing Instructions

You have been asked to provide beta review of the tool 'Adolescent Inclusion Decision Tree'. It is intended to support decision-making of trial sponsors, investigators, health agencies, and/or ethics committees when evaluating the appropriateness for inclusion of adolescents in an adult research trial.

This tool is not designed to establish a minimum "cumulative score" which must be met to allow adolescent inclusion in an adult trial. Rather, this tool is intended to provide a general framework upon which trial sponsors, investigators, health agencies, and/or ethics committees can evaluate attributes of the disease, trial design and/or investigational environment and engage in robust conversation on the appropriateness of adolescent inclusion in relevant trials.

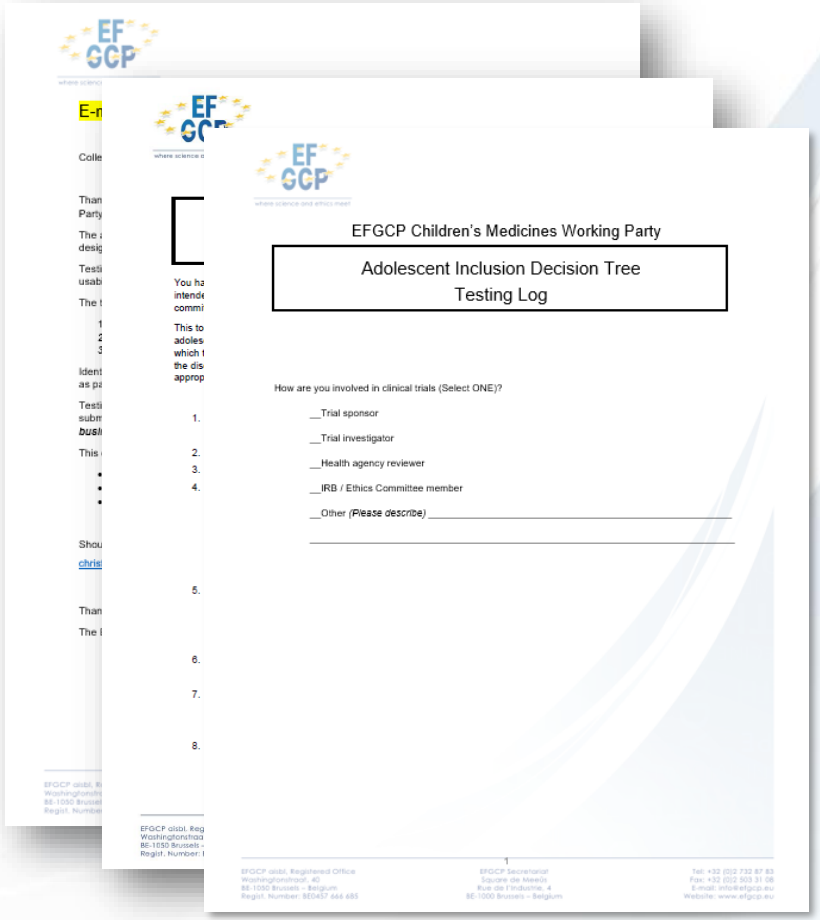
1. You have been provided one (1) copy of the 'Adolescent Inclusion Decision Tree', one (1) copy of the 'Beta-Testing Instructions' (*this document*), and one (1) copy of the 'Testing Log'.
2. Please record all of your observations from this beta-test in the Testing Log.
3. Only those observations captured in the Testing Log will be utilized to refine the Decision-Tree.
4. The Testing Log asks you to record how you are involved in clinical trials:
   a. As a trial sponsor, trial investigator, sponsor, health agency reviewer, IRB or ethics committee member, or other.
   b. If you serve in one or more of these roles (e.g., as an investigator and as a member of an IRB or Ethics Committee), you are asked to SELECT ONLY ONE role and complete the beta-test from that perspective only.
5. The Testing Log is built to capture your perspectives on the:
   a. Overall functionality of the comprehensive tool (*how "useful" is the tool in your role?*)
   b. Interpretability of each component of the tool (*how "understandable" is each component?*)
   c. Overall usability of the comprehensive tool (*how "easy" is the tool to use?*)
6. The Testing Log also includes a section for you to capture any gaps you have identified in the tool. In this section of the Testing Log, please focus on highlighting "critical errors of omission".
7. During beta-testing, questions should be sent to the following mailbox: christina.bucci-rechtweg@efgcp.eu.
8. **Please return completed Testing Logs to the following mailbox**: christina.bucci-rechtweg@efgcp.eu.

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")*

Testing packets included

Testing Log (*pre-defined VAS scoring ,pre-defined to evaluate each 'Focus Area'*)



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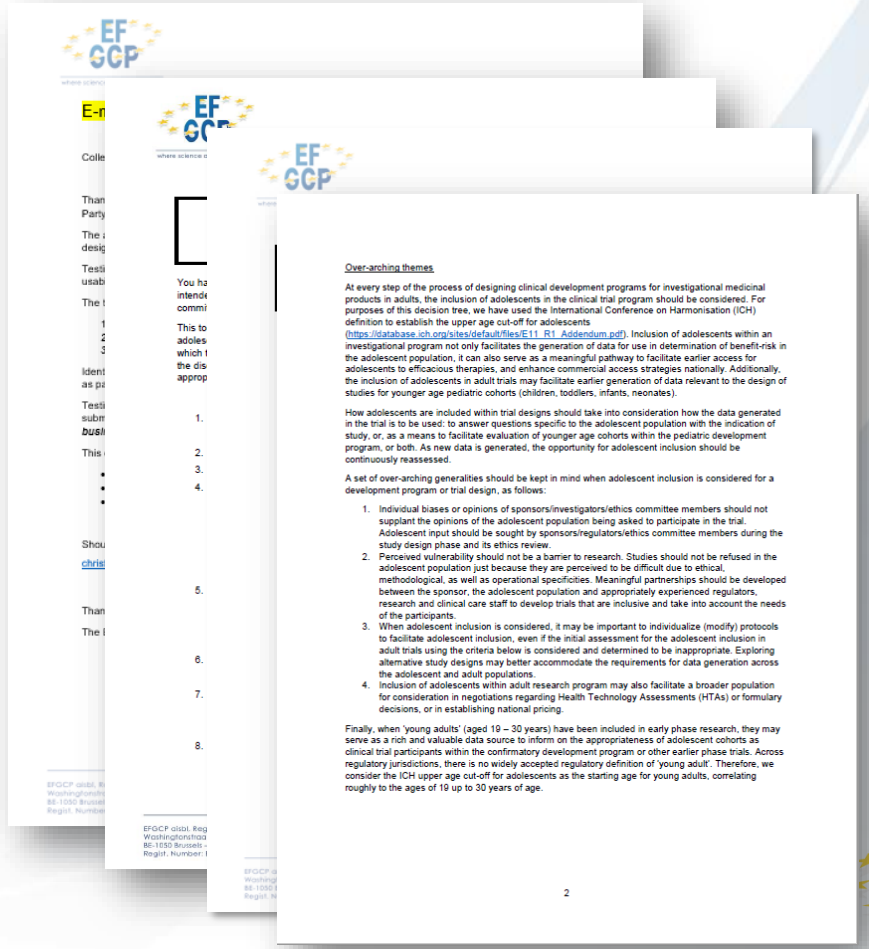
Decision Tree



Beta-testing Findings

- 6 testers returned completed Logs
  - Overall Functionality of the tool rated high (VAS range = 5 [Excellent] – 4 [Very Good])
  - 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)
  - Overall Usability of the tool rated high (VAS range = 5 [Excellent] – 4 [Very Good]) with the exception of one tester (VAS range 3 [Good])
  - No gaps identified
  - 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**

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Acknowledgments

Bryan Michaux (EFCGP), Odile Chantrenne (EFGCP), Ingrid Klingmann (EFGCP), the EFGCP Children's Medicines Working Party

Thank You for your Attention

Dr Martine Dehlinger-Kremer

On behalf of the EFGCP Children's Medicines Working Party 'Adolescent Inclusion in Adult Trials' study team

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