Fortrea

Enrolling adolescents into adult clinical trials

Bringing safe and effective treatments to children and adolescents sooner

Designing late phase (and in some instances early phase) clinical trials to enroll both adults and adolescents, when it is medically, scientifically, and ethically sound to do so, can speed up the access to innovative new medicines in children across all age groups. The decision to combine the enrollment of both adolescents and adults into a clinical trial must be based on the knowledge that the disease, and the anticipated response to therapeutic intervention, are similar enough to justify this approach. In some indications, there is already a trend to include adolescents in adult phase 3 trials; figures from February 2021 from clinicaltrials.gov are quoted as 62% for phase 3 asthma trials (13/21) and 52% for phase 3 atopic dermatitis trials.[1] Various stakeholders have endorsed this approach and regulations and guidelines have been introduced in recent years.

Optimal drug doses and formulations are expected to be different between pediatric and adult patients, however differences in dosing and formulation between adults and pediatric populations are generally more relevant to those under the age of 12 years. In many cases, there is no significant physiological basis to suggest different efficacy or safety profiles for adolescents from adults as drug disposition pathways (such as renal elimination, hepatic metabolism, or transport) reach adult activity levels by 12 years of age. For a number of approved drugs, near identical doses and formulations for adults and adolescents (with consideration for body weight cutoffs) are listed in the labeling with reference to treatment of the same condition, but approval for adolescents repeatedly lagged behind that for adults. A review of drugs approved by the FDA since 2007 for use in adults and adolescents demonstrated that dosing was similar in over 94.5% of instances (87/92 trials) and that the clearance in adolescents can be predicted from data in adults using allometric scaling.[2]

So why include adolescents into adult clinical trials?

Problem: There is on average a 10 year delay for the regulatory approval and labeling of an innovative therapy for children and adolescents when compared to adults.

Cause: This delay is a result of sequential drug development programs where trials involving adolescents and children do not start until after the adult marketing authorization has been approved.

Consequence: The highly common practice of prolonged off-label use of medicines in pediatrics, making the conduct of studies in children after market approval for adults, difficult if not impossible. "Studies throughout Europe have shown that at least one-third of children in hospital and up to 90% of neonates in a neonatal intensive care unit receive such drug prescriptions"[3] which can lead to inappropriate drug formulations, and inferior safety and efficacy of the treatment in children.

Goal: The goal is to shorten the gap between approval for adults and children, thus making innovative, safe and effective new medicines available to children in a timelier fashion.

Advantages: The generation of data in adolescents results in earlier generation of data for the study design, and earlier access to innovative medicines, for younger pediatric cohorts (children, toddlers, infants, neonates). It may also result in safer and more effective dosing in these younger age groups.

The regulatory landscape is shifting

Over time, the accumulation of experience from conducting pediatric trials has resulted in an enhanced comprehension of the parallels and variances in disease characteristics and treatment responses among adult and pediatric populations. These advancements in determining pediatric dosing lend support to the rationale for inclusion of adolescents in adult pivotal trials when appropriate. Such an approach has been endorsed by various stakeholder groups including ACCELERATE (Innovation for Children and Adolescents with Cancer),[5] the Institute for Advanced Clinical Trials (I-ACT), and the European Forum on Good Clinical Practice (EFGCP)—to name a few. This approach is supported by regulatory guidances issued by the ICH, FDA and EMA in accordance with local regulations, and the EFGCP has developed a decision tree that provides helpful considerations for adolescent inclusion in adult research.[4]

The following are key considerations for including adolescents as part of pivotal adult clinical trials:

1. The disease is a continuum between adults and adolescents with no known significant differences in pharmacodynamic responses, disease prognosis or manifestations.
2. The pharmacokinetics of the drug has been characterized in adult patients and is expected to be similar between adolescents and adults (which can be confirmed using modeling and simulation approaches).
3. The efficacy and safety data generated in adult patients support the potential benefits to adolescents, outweighing the risks of inclusion in the phase 3 clinical trials.

In some indications the guidance produced is even more specific and allows for adolescents to be included in adult trials in earlier phases of the development. As an example, the FDA have produced a guideline specifically for oncology entitled "Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials."[7] The guideline recommends that adolescent patients should be eligible for enrollment in adult oncology clinical trials at all stages of drug development when the histology and biologic behavior of the cancer under investigation is the same in, or the molecular target of the drug is relevant to, cancers in both adult and adolescent patients.

Discussions with regulators around this topic need to be started as early as possible as this also has impact on the pediatric study plans required by the EMA and FDA.

Whilst in general there is no significant physiological basis to suggest different efficacy or safety profiles for adolescents from adults, there are nuances that must be considered (discussed below) when including adolescent populations into an adult clinical trial. Understanding these nuances will help design a more inclusive study.

What are adolescents and what characterizes them?

- Adolescents are one of the pediatric age groups as defined per ICH E11 (R1),[6] usually age group between 12 and 16, up to 18 years (depending on country/region).
- This period is characterized of rapid growth (pubertal growth spurt), continued neurocognitive development and sexual maturation.
- Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and may affect final height.
- Medicinal products may also interfere with the actions of sex hormones and impede development; therefore, pregnancy testing, review of sexual activity and contraceptive use need to be discussed.
- Many diseases are 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).
- Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies. Due to an increasing level of understanding and decision-making capacity as well as increasing autonomy and less dependence on caregivers, adolescents may start to assume responsibility for their own health and medication. Noncompliance is a special problem; in clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol and tobacco should be specifically considered.

Ethical considerations

The inclusion of adolescents into adult clinical trials follows the same principles and guidelines for the involvement of all children in clinical research including:

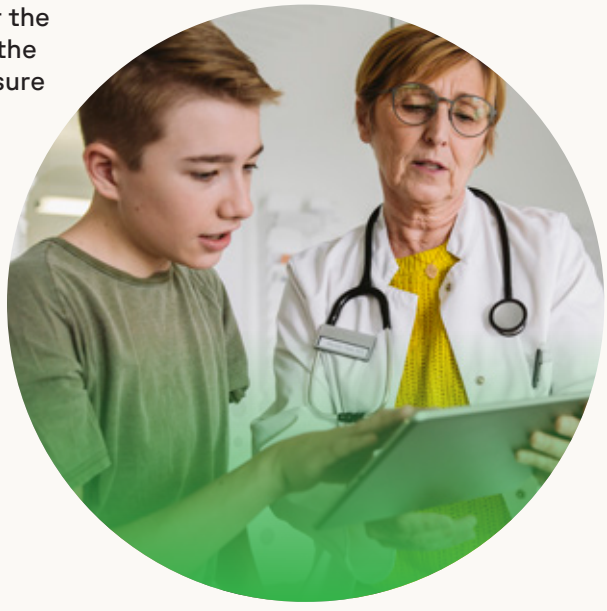
- The premise that the information gained by their involvement in the trial could not be gained by study of adults capable of providing informed consent or by using methods other than a clinical trial
- The potential clinical benefit of the treatment to the adolescent must justify the risks

Operational considerations

- Utilize trial designs, endpoints and assessment schedules that will not unduly exclude adolescents from participation in adult trials
- Consider the impact of country-specific pediatric regulations on the protocol requirements and study timelines, as including adolescents may cause delays in start-up or delays in entering adolescent patients into a study in some countries
- Health care locations and providers for adults and adolescents may be separate and distinct from one another
- Include assent requirements for adolescents according to local requirements and cultural norms
- Privacy is important for adolescents and includes discussions around sexual activity, pregnancy testing and contraception, use of tobacco and illegal drugs

Voice of the patient – what do adolescents think about this topic?

Through our established relationship with the international Children's Advisory Network iCAN (https://www.icanresearch.org/) we were able to conduct a short online survey in March 2023 to gain some insights into this topic. Members of this network aged 12 to 17 were asked for their opinion on being included in an adult trial prior to market authorization in adults. We received 25 responses from adolescents and they raised some really important and valid points. While they thought it was a positive step for adolescents to be included in these earlier adult studies, safety of the treatment was their number one concern. Most said they would consider enrolling in an adult trial, but they all stressed the need for clear and age-appropriate study education, tailored for the parents and the patient. They acknowledge the role of the parent in the decision to enroll but focused on making sure the adolescent is involved and completely understands what they are assenting to. They also talked about the need for additional time, extra support for adolescents, full transparency from the study sponsor and investigators, comfort aids and safe spaces to support adolescents in trials.



How can we at Fortrea support your pediatric program?

Fortrea has gained extensive experience in conducting pediatric trials over the past decade, including studies enrolling adolescents into adult trials. A team of well-versed medical and operational SMEs, our Rare Disease, Advanced Therapies and Pediatrics Team, as well as our regulatory experts are here to support the strategic planning and conduct of your pediatric development program across all pediatric age ranges including adolescents.

References

1. Noel GJ, Nelson RM, Bucci-Rechtweg C, et al. Inclusion of Adolescents in Adult Clinical Trials: Report of the Institute for Advanced Clinical Trials for Children's Pediatric Innovation Research Forum. *Ther Innov Regul Sci* 55, 773–778 (2021). https://doi.org/10.1007/s43441-021-00283-y.
2. Momper JD, Mulugeta Y, Green DJ, et al. Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr.* 2013;167(10):926–932. DOI: 10.1001/jamapediatrics.2013.465.
3. Gore R, Chugh PK, Tripathi CD, Lhamo Y, Gautam S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. *Current Clinical Pharmacology*. 2017 ;12(1):18-25. DOI: 10.2174/1574884712666170317161935. PMID: 28322168.
4. Decision tree from EFGCP can be downloaded here: https://efgcp.eu/working-party?wp=CMWP.
5. Gaspar N, Marshall LV, Binner D, et al. Joint adolescent–adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform—ACCELERATE. *Ann Oncol*. 2018;29(3):766–771. DOI: 10.1093/annonc/mdy002.
6. ICH E11 (R1) retrieved here: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf.
7. FDA Guidance (2019) Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. Retrieved here: www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-inclusion-adolescent-patients-adult-oncology-clinical-trials.

LEARN MORE at fortrea.com

Fortrea