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ANALYTICAL REPORT

Inclusion of Adolescents in Adult Clinical Trials: Report of the Institute for Advanced Clinical Trials for Children's Pediatric Innovation Research Forum

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Abstract

Including adolescents in adult clinical trials can play an important role in making innovative new medicines available to children in a timelier fashion. Stakeholders involved in the processes leading to regulatory approval and labeling of new drugs recognize that challenges exist in involving adolescents and older children in clinical trials before the safety and efficacy of these drugs are established for adults. However, it has been possible to design and execute phase 3 trials that combine adults with adolescents which are medically and scientifically sound and ethically justified. Based on this experience and considerations of the medical and scientific, ethical, and operation-related matters, the 2019 Pediatric Innovation Research Forum advocated for the position that adolescents routinely be considered for enrollment in phase 3 clinical trials. The Forum also concluded that exclusion of adolescents in adult pivotal trials occur only when a thorough evaluation of the target disease and the potential benefit and risks of the study intervention supports a delay in their involvement until after completion of clinical trials in adults.

Keywords Pediatrics · Clinical trials · Adolescents · Drug development · Phase 3 trials

Introduction

The average time between regulatory approval and labeling of an innovative therapy for adults and children is nearly a decade [1]. This delay can be the result of sequential rather than integrated development programs where trials involving children do not start until after the adult marketing authorization. The consequence of this approach can be prolonged off-label pediatric use, making the conduct of studies in children after market approval difficult if not impossible [2]. Early planning for pediatric trials, careful evaluation of the disease similarities across age groups to facilitate extrapolation, and the use of innovative methodologies, such as model-informed drug development and innovative statistical approaches are all being used to address this challenge [3]. Another approach that has been routinely utilized in conditions, such as asthma and HIV/AIDS is the inclusion of adolescents either in adult trials or in adolescent trials conducted contemporaneously with adult Phase 3 studies. A February 2021 review of clinicaltrials.gov indicates that adolescents are eligible to enroll with adults in 23% (43/185)

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of phase 3 interventional trials involving patients with either asthma, atopic dermatitis, hypertension, inflammatory bowel disease or SARS-CoV-2 infection. For some indications, the majority of phase 3 trials (62%, 13/21 for asthma and 52%, 11/21 for atopic dermatitis) are enrolling adolescents with adults. This trend aligns well with recent recommendations from the European Forum on Good Clinical Practice (EFGCP) [4] and has been supported by regulatory guidance that have been issued by FDA, EMA and ICH. (Table). However, implementation of adolescent inclusion in adult trials brings unique considerations and challenges, which in turn has limited widespread use of this approach to date.

In October 2019, the Institute for Advanced Clinical Trials (I-ACT) for Children convened a workshop that invited a diverse group of stakeholders. The group reviewed the regulatory, scientific, ethical, and operational considerations related to advancing early inclusion of adolescents in clinical development and recommended ways that challenges might best be addressed. This report summarizes deliberations and recommendations from this Forum. For the purposes of this review the group adopted the position of EFCGP [4] "… 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 …"

Medical and Scientific Bases That Support Combined or Parallel Adult–Adolescent Trials

Similarity of the Target Disease in Adults and Adolescents

Central to decisions regarding combining adolescents and adults in a trial or in conducting adolescent and adult trials in parallel is understanding that the disease and the expected response to therapeutic intervention are sufficiently similar. This has usually been determined based on the clinical observations, the natural history of disease and the influence of therapy on signs and symptoms attributed to the disease. For some rare diseases [5–7], combining adolescent and young adults can be strongly supported by the similarity of the disease process, the need for collecting experience with an innovative intervention in a disease that is very rare and the urgent need to influence progression of a disease with a very high morbidity and mortality. Outside of these unique circumstances, this assessment of similarity, often used by clinicians to prescribe drugs off-label, is now being used to make decisions regarding pediatric drug development that are based on the extrapolation of results generated in adult clinical trials to children [8]. In recent years, advances in understanding the molecular basis for disease and the scientific rigor applied to defining drug targets has increased confidence in assessing the similarities related to efficacy and response to therapies between adult and adolescent patients. These advances have been reflected in the regulatory guidance (Table 1) that provide the medical rationale for conducting combined trials in specific therapeutic areas and for specific diseases. As advances continue to be made in understanding disease pathophysiology and therapeutics underpinning these recommendations should be used to increase the frequency of combined adult–adolescent trials in therapeutic areas and for specific diseases where these trials are not occurring currently.

Pharmacokinetic Considerations

The similarity of the pharmacokinetics of drugs and therapeutic proteins between adolescents and young adults is an important component of the scientific rationale supporting combined adult–adolescent trials. A review of drugs approved by FDA since 2007 for use in adults and adolescents demonstrated that dosing was similar in over 94.5% (87/92) of instances and that the clearance in adolescents can be predicted from data in adults using allometric scaling [9]. These observations support conclusions that allometric scaling could be used to identify initial dosing regimens for adolescents and that pharmacokinetic studies in adolescents may often not be needed prior to initiation of efficacy/safety trials when there are sufficient data obtained in adults to derive dosing estimations. Similar conclusions were supported by work focused on oncologic agents [10] and in a study that used allometric scaling to predict adolescent dosing in 97% of the British National Formulary for children 2006 [11]. Taken together this experience underscores that for many clinical development programs, the data needed to identify pharmacokinetic parameters for adolescents will be available as phase 2 trials are completed in adults. It follows that these data can be used to transition to later stage trials involving adolescents near to, or at the same time that this transition is occurring with adults. Given this recent experience it seems likely that many obstacles related to therapeutic dose selection in adolescents can be avoided, and that the consideration of inclusion of adolescents in combined trials will likely be more dependent on matters unrelated to pharmacokinetics.

Safety and Tolerability

Although the comparability of the pharmacokinetics of a drug candidate between adult and adolescents can provide confidence that drug exposure will be similar, this does not necessarily mean that a given exposure will result in similar safety and tolerability profiles in adults and adolescents. In general, preclinical animal models have been effective in identifying toxicity issues in adults and children older than

Table 1 Selected examples of regulatory guidance and documents indicating the acceptability of including adolescents and older children in adult clinical trials

Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials	March 2019	https://www.fda.gov/media/113499/download
Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients (draft)	July 2020	https://www.fda.gov/media/121318/download
Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs (draft)	June 2019	https://www.fda.gov/media/127712/download
Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry (draft)	August 2018	https://www.fda.gov/media/115172/download
General Clinical Pharmacology Considerations for Pediatric Studies (draft)	December 2014	https://www.fda.gov/media/90358/download
Pediatric HIV Infection: Drug Product Development for Treatment	March 2019	https://www.fda.gov/media/113319/download
Rare Diseases: Common Issues in Drug Development (draft)	January 2019	https://www.fda.gov/media/119757/download
Influenza: Developing Drugs for Treatment and/or Prophylaxis	April 2011	https://www.fda.gov/media/73339/download
Uncomplicated Gonorrhea: Developing Drugs for Treatment	August 2015	https://www.fda.gov/media/88904/download
E11 Clinical Investigation of Medicinal Products in the Pediatric Population (2000)	December 2000	https://www.fda.gov/media/71355/download
E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (2018)	April 2018	https://www.fda.gov/media/101398/download
S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines	September 2018	https://www.fda.gov/media/101398/download

12 years and additional preclinical toxicology data are often not required to start trials involving adolescents [12]. Concerns about estimating similarity of safety and tolerability between adults and adolescents have included consideration of how endocrinologic changes associated with puberty and normal neurologic and physiologic development might influence off-target effects of drugs. These concerns can often be addressed sufficiently by confirming the mechanism of action of a drug and the molecular basis of interaction of drug with human tissues. Experience with use of drugs belonging to the same class or that have the same therapeutic target might be helpful in identifying the importance of this influence and provide confidence that an untoward effect related to physiologic changes of puberty will be unlikely [13] or, alternatively, serve as the basis for requiring that this influence be monitored in adolescents [14, 15].

Trial Design Considerations

The rationale for a combined adult–adolescent trial also needs to consider factors that impact the trial design. These factors include the acceptability of using the same trial endpoints, the choice of the comparator, and the use of invasive and other protocol procedures in adults and adolescents to assess efficacy and safety. If primary endpoints and findings related to safety and tolerability cannot be assessed in the same manner for both adults and adolescents in a combined study population, conducting a combined trial may not be appropriate. In this circumstance, it may be preferable to conduct parallel trials in adults and adolescents.

Forum Conclusions

The medical and scientific rationale for combined adult–adolescent trials depend largely on evidence supporting the similarity of the target disease and the response to therapy between adults and adolescents. Advances in the understanding of targeted diseases in modern drug development often permit an informed decision on this similarity and have been the basis for encouraging inclusion of adolescents in late-stage clinical registration trials that in the past would have restricted enrollment to adults. These trials can be designed as combined trials involving adults and adolescents or as trials involving adolescents conducted in parallel to phase 3 trials involving adults. Although circumstances will occur where neither combined nor parallel trial approaches can be justified, this conclusion should be reached only after the medical and scientific bases for this justification is thoroughly considered.

Ethics of Including Adolescents in Early Clinical Trials

The ethical inclusion of adolescents in a clinical trial needs to consider the same principles that have guided the involvement of all children in clinical research [16]. These principles include 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. In addition, the potential

clinical benefit of the treatment to the adolescent must justify the risks [17].

The similarity of disease and the likely response to therapy between adults and adolescents that is central to the rationale for combined adolescent–adult trials should play a role in considering the ethics of involving adolescents in these trials. Where there is great certainty that the target disease and the response to therapy will be the same in adults and adolescents, the inclusion of adolescents in a clinical trial with adults may be difficult to justify, especially if that trial is placebo controlled. In this case the results obtained in adult patients would be sufficient to establish the efficacy of the therapeutic intervention for adolescents. This degree of certainty should be sufficient to support extrapolation of results of efficacy trials in adults to adolescents. This, coupled with the collection of safety data in adolescents, should warrant regulatory approval and labeling of a new therapy for adolescents. However, this circumstance is unlikely to occur before phase 3 trials are completed for most new therapies and there will be a need to have experience in treating adolescents before this certainty exists. For therapies where combined trials have proceeded, the prospect of clinical benefit for an adolescent patient is determined by preliminary efficacy data collected in studies that involve adults. When this benefit justifies the risk of the intervention, delaying the study of the therapy in adolescents may be difficult, if not impossible, to accept [18]. This circumstance often occurs where therapy may be lifesaving or addresses severe morbidity. By proceeding with a combined adult–adolescent trial in phase 3 of development, information can be generated which will support the assessment of potential benefit and risk in adolescents and provide the basis for prompt regulatory approval and labeling for appropriate use of these innovative therapies much earlier for children than would have occurred if adolescents were excluded from phase 3 trials.

Forum Conclusions

The inclusion of adolescents in combined trials is appropriate when widely accepted ethical and scientific principles of involving children in clinical research are followed. The recent experience of involving adolescents in combined trials and an ethical framework for assessing this involvement support a position that every new therapy should consider involving adolescents in phase 3 development. Exclusion of adolescents from pivotal phase 3 adult trials or not conducting concurrent trials in adults and adolescents should only be acceptable in circumstances when the potential benefit and risk of the therapy can be established for adolescents by trials restricted to adults or when assessment prior to phase 3 indicates that the risk of including adolescents in combined or concurrent phase 3 trials is greater than the potential benefit that the study intervention offers.

Operational Issues Posed by Involving Adolescents in Initial Phase 3 Trials

Ethical and medically sound combined adult–adolescent clinical trials can face substantial challenges related to operational aspects of trial execution. It is not uncommon for health care locations and providers for adults and adolescents to be separate and distinct from one another. This separation is often cited as a major obstacle for considering these trials. Although each trial will have its unique set of operation-related challenges, the importance of completing these trials should provide ample motivation for addressing them.

Although combined adult–adolescent trials have been successfully completed in therapeutic areas where clinicians deliver routine care to both trial eligible adults and older children, the circumstance of having adults and adolescents receiving routine care for a target disease need not be a prerequisite for designing and executing a combined trial. Engaging patients, caregivers, physicians, and health care systems can help to improve collaboration between investigators, patients and the pediatric and medical practices that are affiliated with trial sites interested in participating in clinical research. It can be the case that such collaboration could establish clearer paths for the appropriate transition of health care from a pediatrician to an internist and provide patient benefits that extend beyond their involvement in a clinical trial. In circumstances, where inclusion of adolescents in trials is considered to require involvement of separate sites or trial protocols because of different study endpoints or protocol procedures, parallel conduct of adult and adolescent trials may be more appropriate. This parallel trial conduct approach can achieve the same desirable effect of gaining the necessary information for simultaneous approval and labeling of new products in adults and adolescents.

A frequently discussed obstacle, based on the anecdotal experience, is that inclusion of adolescents may slow the timeline to achieve last patient visit during phase 3 trial enrollment. This obstacle is difficult to understand for some target diseases (e.g., asthma, sexually transmitted diseases) where trial eligible adolescents may contribute a substantial proportion of the overall eligible patient population based on the epidemiology of the disease. Concern that differences in the informed consent process between adults and adolescents, and the need for including an assent process when enrolling adolescents leads to less efficient patient enrollment in a combined trial, is also difficult to understand. These challenges deserve closer analysis before accepting that combined adult–adolescent trials complicate phase 3 development and contribute to delayed approval of innovative new therapies.

The recent experience of excluding adolescents in many of the COVID-19 related clinical trials [19] despite the similarity of the disease in adolescents and young adults, and the potential for life-saving benefit of these therapies, suggests that the initial reluctance to conduct combined adolescent–adult clinical trials may have been, in part, related to concerns that presumed, rather than real, obstacles related to including adolescents would delay clinical development. As the pandemic evolved, it became more common to include adolescents in phase 3 trials aimed at assessing treatment of patients with SARS CoV-2 infections [20]. Currently, 7% (7/96) of phase 3 trials listed on clinicaltrials.gov that are assessing innovative interventional treatments for SARS CoV-2 infection are co-enrolling adults and adolescents. Such experience underscores the need for collecting data related to the efficient conduct of combined adult–adolescent trials and the importance of basing decisions not to proceed with ethical and medically sound trials because of assumed, or addressable challenges that may be part of combined adult–adolescent trials.

Forum Conclusions

Differences between adults and adolescents related to the location of health care delivery and to the health-care providers responsible for these two patient groups are likely to be identified as challenges to operationalizing combined adult–adolescent clinical trials. Other obstacles that have been raised that include inherent differences in rate of enrollment and difficulty in obtaining informed consent for adolescent patients, deserve closer scrutiny. Conclusions related to the impact of these challenges on executing combined trials should be based on the data rather than anecdotal experiences. It can be expected that as combined adult–adolescent trials become more common, the operational challenges currently recognized will have solutions identified that can serve as best practices for incorporation in the future adult and adolescent combined trials.

Conclusions

Inclusion of adolescents in adult clinical trials or the conduct of parallel adolescent trials represent important methodological approaches to advance drug development in pediatric patients when justified scientifically and ethically. This should be considered the default position in innovative product development. Restricting initial phase 3 development to adults should be based on there being (1) substantial differences between adults and adolescents regarding the pathophysiology of the target disease or the anticipated response to the study therapy, (2) confidence that efficacy experience in adults alone combined with safety data in adolescents would justify regulatory approval and labeling of a new product for use by adolescents, or (3) a risk of inclusion of adolescents (based on the preclinical or clinical experience in adults) that cannot be justified given the potential benefit of the therapy being studied.

Author contributions

Drs. Noel, Hovinga and Connor prepared the initial draft of the manuscript. Drs. Nelson, Bucci-Rechtweg, Portman, Miller, Moreno, Green and Snyder provided critical intellectual content by providing edits and comments that led to the final version of the manuscript. The authors acknowledge the contribution of all stakeholders who participated in the Forum and the contributions of The Collaborative Network for European Clinical Trials for Children (conect4children or c4c; an action under the Innovative Medicines Initiative 2 (IMI2) Joint Understanding (https://www.imi.europa.eu), Grant Agreement 777389) and for reviews of the manuscript by Drs. Yeruck Mulugeta, Gregory H. Reaman and Margaret Gamalo.

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Declarations

Conflict of interest

None of the authors have competing interests that would undermine the objectivity, integrity, or perceived value of the information communicated in this manuscript. The opinions expressed in this article are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration.

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