

# Standard 6: Age Groups for Pediatric Trials

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## KEY WORDS

age group, age-related analysis, age-related stratification, pediatric, randomized trials, StaR child health

## ABBREVIATIONS

RCT—randomized controlled trial

SSRI—selective serotonin reuptake inhibitor

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This is the sixth in a series of standard articles resulting from an ongoing process in which a group of invited experts called a Standard Development Group from StaR Child Health assembles and exchanges information about methods for pediatric trial design, conduct, and reporting. More detailed information about this topic can be found in the introductory article of this supplement or at the StaR Child Health Web site ([www.starchildhealth.org](http://www.starchildhealth.org)).

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## DILEMMA

It has long been an axiom in clinical pediatrics that “children are not just little adults.” It has also been recognized that there are many changes from birth through childhood and the adolescent years. However, the full implications of pediatric age groupings for health care and research are still not adequately understood. There is still much to be discovered about children’s biological and psychological development and how these processes affect the effectiveness and efficacy of interventions. Trial design that accounts for age differences and promotes consistency in reporting of age-related data is essential to ensure the validity and clinical usefulness of pediatric trial data.

A recent study highlighted variable treatment efficacy in children versus adults. In this study, 128 meta-analyses from Cochrane reviews, containing data on at least 1 adult and 1 pediatric randomized controlled trial (RCT) with a binary primary efficacy outcome, were reviewed.<sup>1</sup> The authors found that in all except 1 case, the 95% confidence intervals could not exclude a relative difference in treatment efficacy between adults and children of >20%; in two-thirds of these cases, the relative difference in observed point estimates was >50%. The study also highlighted the paucity of RCTs in pediatrics; the median number of children per meta-analysis was 2.5 times smaller than the number of adults.

Children and adults seem to have distinctive responses to treatments. For example, administration of phenobarbitones is useful for adults with cerebral malaria and is associated with decreased convulsions. However, in children, this drug is associated with increased 6-month mortality. Similarly, corticosteroids may offer survival benefit for adults with bacterial meningitis but not for children with the same condition. In acute traumatic brain injury, corticosteroids did not decrease mortality in adults, but there was a trend for increased mortality in children.<sup>1</sup> In asthma, long-acting  $\beta_2$ -agonists decreased exacerbations in adults but tended to increase exacerbations in children.<sup>1</sup> Intravenous lorazepam, when compared with diazepam in status epilepticus, led to significantly more discontinuations of status in adults but not in children. It is not surprising then that although using an algorithm for extrapolation of adult data for use in pediatric drug licensing and development was found to be useful for streamlining drug development and approvals for pediatric use, complete extrapolation from adult data were only appropriate for 6% of drugs reviewed.<sup>2</sup>

Beyond the stark contrast in the efficacy of pharmacologic interventions between children and adults, considerable variation of adverse events and morbidity can be anticipated across the pediatric age range. Authors of a recent study of pediatric drug surveillance and adverse event reporting concluded that “suspect drugs and adverse events should be evaluated in the context of age groups” because both drug utilization and the ability to report adverse events vary by age.<sup>3</sup> For example, there has been a recent report of excess asthma-related events attributable

to long-acting  $\beta$ 2-adrenergic receptor agonists in children, with the highest incidence of adverse events in the 4- to 11-year-old age group.<sup>4</sup> New safety information arising from studies performed under the auspices of the Pediatric Exclusivity Program in the United States confirms that adverse events differ in children compared with adults, and availability of additional information about children led to safety labeling changes in 26% of drugs reviewed.<sup>5</sup> Postapproval reporting of adverse events for 1 year in children, which has occurred in the United States because of the Best Pharmaceuticals for Children Act, led to changes in recommendation for >30% of drugs, and several of the adverse events revealed were rare and life-threatening.<sup>6</sup>

It is well known that children's rapid growth and development provide a unique context for health care delivery.<sup>7</sup> For example, longitudinal studies of children's health care use and morbidity indicate that health care use and the number of acute diagnoses steadily declines from infancy to adolescence. In contradistinction, the rate of psychological diagnoses peaked during 2 transition periods in child development: early elementary school and early adolescence.<sup>8</sup> Even within a uniquely defined age group, variable responses to treatment are complex. We know that neonates (preterm and term) are an extremely heterogeneous group. During the neonatal period, pharmacokinetic and pharmacodynamic parameters change continuously. Consequently, medication dosages and administration intervals must be adjusted frequently and individualized for each patient.<sup>9</sup> For procedural pain management, oral sucrose has been shown to be very effective for neonates and somewhat effective for young infants; however, effectiveness for older infants and children is still unsupported in many instances.<sup>10,11</sup> In

general, bronchodilators are less effective at younger ages for a variety of etiologic and physiologic reasons.<sup>12</sup> Differences in adverse events for variable age groups of children are also well documented. For example, the majority of cases of Reye's syndrome occur in children aged <6 years, and nearly all cases emerge in children aged <12 years.<sup>13</sup> Another example is teeth staining with tetracyclines, which does not occur after the age of 12 years.<sup>14</sup>

Regarding effectiveness of nonpharmacologic treatments, it is known that cognitive behavior therapy is only effective for children with sufficient cognitive ability, which is usually present from the age of 8 years. For example, neonates experiencing pain can benefit from sensory stimulation such as rocking, swaddling or sucking, and maternal interventions such as maternal odor, voice, and skin-to-skin contact.<sup>15</sup> For 3- to 5-year-olds, simple guided imagery, distraction, preparation, and play therapy can be effective anxiolytic/analgesic interventions. Younger infants are less likely to benefit from these strategies, and older children require more complex approaches in accordance with their language, cognitive, behavioral, and emotional development.<sup>16,17</sup> These examples illustrate that the outcome of interventions for patients aged 0 to 18 years may differ across this age span due to a mix of biological, developmental, and psychosocial characteristics.

Surprisingly, there seems to be no guidance for child health trialists in identifying appropriate age groups for trials and age-based analyses. As a result, there are discrepancies in how age groups are defined in published trials; as such, we have collated information from trials and systematic reviews (see the StaR Child Health *Technical Report* within this series). For example, in 3 trials regarding childhood obesity published in *Pediatrics* in 2011, there were 3 different age groups used: 8 to 16

years,<sup>18</sup> 5.5 to 9.9 years,<sup>19</sup> and 5 to 9 years.<sup>20</sup> Although some variation in age groups could be justified for different types of treatment (parent- versus child-directed), the age differences may create problems for comparison of outcomes and data synthesis, if appropriate. For autism, a neurodevelopmental disorder, we know that the behavioral manifestations of autism can change from preschool to adolescence. These changes couple with changes in brain development that occur. Autism trials that include wide age ranges may blur important differences between specific age groups, if they exist, and risk over- or underestimating safety and effectiveness for some children. Nevertheless, of the 14 trials in an autism systematic review,<sup>21</sup> only 4 addressed age groups with an age range of <5 years.

Another example of lack of consistency and clinically meaningful age groups was demonstrated in 2 eczema systematic reviews.<sup>22,23</sup> We know that eczema presents differently in infancy from later childhood, both in terms of its appearance and likely causes. Infants and older children have differing bowel flora, which is less amenable to alteration with increasing age. It is therefore possible that the effectiveness of probiotics could vary for these different age groups. Moreover, educational and behavioral interventions are expected to vary across age groups, with increasing child involvement at the older ages. It is therefore likely that age-treatment interactions of narrower age groups would facilitate more targeted assessment of effectiveness of interventions. However, of 17 trials included in 2 systematic reviews of eczema/dermatitis, only 3 used subgrouping by age, and these age ranges varied from <1 year to 12 years, with wide variability in the age boundaries used.

Conversely, in some domains there may already exist greater consensus on

what would be the appropriate age groups to use. For example, a systematic review of selective serotonin reuptake inhibitors (SSRIs) for depression showed high consistency of age groups used in separating children from adolescents.<sup>24</sup>

### AGE GROUPS AS PROXIES FOR BIOLOGICAL, DEVELOPMENTAL, PSYCHOLOGICAL, AND SOCIAL DIFFERENCES

The use of age-based groups is a “proxy” marker of many complex and interacting biological, developmental, psychological, and social changes that occur from birth to adulthood. Age groups have been used for population health, clinical care, and research for decades, and variable age groups have been recommended by a number of agencies and by biological, developmental, and psychology experts as indicators for the timing of important changes. Age groupings are also used for educational and health care systems as an indication to suitability for entry. In addition, age groups exist for many tools that measure development and psychological function, and many biological tests have age-based reference standards for results.

Age groups have been used as a marker of exposure or proxy for important biological, developmental, and psychological stages because measuring all of these factors accurately on an individual basis is often impossible, impractical, or too costly. There are also many settings in the world where measurement of these factors is not possible because of resource or logistical issues. Grouping children according to age can provide a practical advantage over more complex methods of assessment for use by clinicians, services, and caregivers when deciding treatment suitability. Also, prioritizing 1 aspect of biological development over others or over psychological development may not be possible for all trials, especially in trials looking at less targeted interventions and in which

a range of outcomes are important. Therefore, age-based groupings may help identify important differences and similarities across childhood and youth, and this knowledge may need to be taken into account when considering the effectiveness of interventions.

Conversely, it should be acknowledged that age may sometimes be only a crude correlate of the biological, developmental, and psychological factors of interest. In these cases, direct evaluation of these factors may be more informative, whereas using only age-group analyses may yield misleading results due to ecological fallacy and other biases. For example, in a sample of children with intellectual disability, the participants’ functional age might be more important than their chronological age as a factor that predicts the outcome of a behavioral intervention. Similarly, in a trial for effectiveness of growth hormone, bone age and pubertal status will be more important than chronological age. However, in trials of children with normal IQ and trials in conditions for which pubertal status and bone age are not known to be key determinants of outcome, chronological age is a sufficiently good marker for physiologic, developmental, psychological, and social stage. Chronological age will likely be adequate therefore in designing many, if not most, pediatric randomized trials. However, for trials in conditions in which well-validated and well-performing multivariate predictive models exist for the outcomes of interest,<sup>25</sup> it may be preferable to perform risk stratification and evaluation of risk–treatment interactions using the full validated multivariate models.<sup>26</sup>

### POTENTIAL REASONS FOR DIFFERENT MEASURED TREATMENT EFFECTS ACROSS AGE GROUPS

The medical treatment of children should be based on evidence developed

through RCTs performed with children as participants, with appropriate consideration of age strata in design and analysis. If there is a real age-related difference in treatment effect, this could either reflect differences in baseline risk of the outcomes of interest and/or reflect differences in the relative treatment effects for physiologic, developmental, psychological, or social reasons. In this case, the reason for that difference in effect, if unknown, could be explored to identify the underlying mechanism. For example, cognitive behavior therapy may be effective in older children but not young children because it relies on a level of intellectual maturity; or a drug may be effective in older children but toxic in neonates because it relies on the maturity of an enzyme pathway for its metabolism.

These differences need to be considered in the design of clinical trials in terms of defining the optimal age window for eligibility criteria and whether age stratification in randomization or adjustments and/or testing for age–treatment interactions in the analysis plan are needed. Trials would need to consider upfront previously known and well-validated age-related differences. Trials may be used also to test hypotheses about new, postulated age-related differences. It should be noted that both undervaluing as well as overemphasizing age-related differences could be harmful. For example, if there are strong age–treatment interactions, trials that study children at different age levels may reach opposite conclusions, and trials that include an inappropriately wide age range may reach spuriously null conclusions or an average estimate of effect that is an overestimate for some age groups and an underestimate for others. Conversely, if eligibility criteria are inappropriately restricted to a narrow age window based on unfounded considerations, this will result in a study that is underpowered to detect true differences

if they exist. Spurious subgroup differences may also arise in evaluations of age-specific strata, especially when done post hoc and with no clear rationale and under conditions of extensive multiple testing, as has been shown repeatedly for many claims of interactions.<sup>27–29</sup>

Alternatively, it could be that age-related differences in treatment effect have been measured because of the study design, such as use of an intervention factor (eg, dose or method of delivery), outcome measure, comparator, or duration of follow-up that is inappropriate due to important differences in physiology, development, psychology, or social context between the groups. For example, the use of a respiratory outcome measure (eg, peak flow) that cannot be reliably measured for all age groups could change the effect size for some child age groups and therefore not be a true indication of effectiveness; another example is administration of an intervention to modify a behavior (eg, diet or exercise) to the parents of a young child may be more or less effective than administration of the intervention directly to an older child or adult.

Another possibility is that it may not be considered appropriate to administer the same comparator to all age groups, and the use of a different comparator may change the effect size. For example, children may be offered a play session, whereas adolescents would be offered an interview or reading material for behavioral interventions, and the play session may influence the outcome differently to the alternative comparator. In this example and others, it is possible that 1 or more interactions occur between methodologic issues and biological, developmental, psychological, or social systems at different ages.

## USING EVIDENCE TO MAKE DECISIONS

Optimal health care decision-making depends on the totality of the available

evidence, which can include many trials and their respective systematic review and meta-analysis. When combining data from several pediatric trials, information may be lost if there are major differences in the age groups used for the included trials but data are not available in sufficient detail to address these differences. Faced with this sort of evidence, clinicians are not able to make sensible decisions for individuals. In an environment in which more pediatric evidence is needed and pediatric trials often have low sample size, combining data from existing trials becomes increasingly important.<sup>30,31</sup> Age-treatment interactions are likely to be more reliably detected when data can be harmonized and combined across many trials. However, few systematic reviews currently have the benefit of using the raw data with detailed information on age and outcomes from all participants. Usually, published trials provide either no separate data for age strata or report age-related data haphazardly (means or medians compared with age distribution) and with different cutoffs across trials, thus making it difficult to probe consistently into age-related differences.<sup>32</sup> The flip-side to this problem, which is less commonly seen, is the presentation of evidence for such a narrow age group that it cannot safely be applied to children of different ages.

It is therefore necessary, when designing RCTs in child health, to ensure that the age groups in the trial are designed to bring together children and young people who are more alike than they are different and/or take differences explicitly into consideration in the design and analysis. Ensuring consistency across groups studied in different trials will build a more solid base of evidence about how interventions affect children at particular ages.

## OPPORTUNITIES IF CONSISTENT AGE GROUPS ARE USED

In the absence of a body of research and clear guidance in this area, currently

we can only envisage the ideal state for child health research in which the same age groups are used consistently across trials for interventions for a particular condition. This would enhance decision-making because using consistent age groups to make decisions about inclusions and subgroup analyses in pediatric trials will make it possible to explore age-treatment interactions consistently for a range of interventions. This sort of evidence is needed to support use of broad or narrow age bands. We know that some differences which are related to one factor will not always be predictable; moreover, interactions of the many factors for which age is a crude proxy measure (eg, puberty, cognitive level) and the impact of that interaction on outcomes are hard to anticipate. Trials included in the systematic review of SSRIs for depression<sup>24</sup> have used similar age groups and are drawing on established wisdom about late childhood and adolescent development to identify groups of children who are likely to have differing drug responses, both positive and adverse. It is uncertain whether subtle variations in age groups (variations of 1 year at the boundaries) would make any difference to the effectiveness or adverse effects of treatments or the way those are measured. One study did split an age group into 2 ranges (12–15 years and 16–19 years) but whether that will contribute to our understanding of the safety and effectiveness of SSRIs in children and young people is not yet known. However, the use of relatively consistent age bands will have made decision-making for different age groups easier. The ability to address age-related questions would also be enhanced markedly if raw data from clinical trials became available. This would allow harmonizing age-related analyses across trials that may have used different age-related eligibility criteria and stratification schemes. However, raw data are currently becoming available only for a few trials. An

intermediate solution, the availability of detailed results in trial registries,<sup>33</sup> would also be greatly enhanced by standardization of age-related information.

**GUIDANCE**

**Trial Planning**

In designing a trial, decisions about inclusion of age groups and whether to conduct subgroup analyses based on age groups should be planned in advance. In resource-poor settings, some countries do not have methods in place to record all births, and a child's age can be uncertain. In this situation, trialists should record the method used for ascertaining age, such as caregiver report. To reduce the possibility of a measured treatment effect difference for different age groups that is due to trial design or biases and that does not reflect a true age–treatment interaction, we suggest using the schema as displayed in Table 1. By using this table, place a tick in any cell if there are known or hypothesized differences for biological, developmental, psychological, or social context across the age range of childhood that may affect the choice of optimal study design features. If any cell is ticked, then careful consideration of age groups for inclusion or analyses is warranted.

If age–treatment interactions are already known, then the use of age groups for which homogeneous outcomes are expected would also be recommended. If such interactions are hypothesized and are considered important to demonstrate, the design and analysis plan should maximize the power to detect such interactions.

**Age Groups for Study Inclusion and Subgroup Analyses**

As a starting point for establishing consistent age groups in RCTs, we propose that trialists use the proposed integrated age groups (Table 2) developed by the *Eunice Kennedy Shriver* National

**TABLE 1** Schema for Considering the Likely Impact of Age Group Differences on Trial Design

Feature	Biological <sup>a</sup>	Developmental <sup>b</sup>	Psychological	Social Context and Expectations
Type of intervention (eg, dose, delivery)				
Type or measurement of positive effects				
Type or measurement of harms and adverse effects				
Comparator (eg, type, dose, delivery)				
Duration of follow-up				

Place a tick in any cell indicating known or hypothesized differences for biological, developmental, psychological, or social context across the age range of childhood that may affect the choice of optimal study design features. If any cell is ticked, then careful consideration of age groups for inclusion or analyses is warranted.

<sup>a</sup> Including physiologic, immunologic, and puberty and reproduction factors.

<sup>b</sup> Including educational setting.

Institute of Child Health and Human Development in the United States.<sup>34</sup> These age groups match closely to those outlined by other experts and were developed by consulting with what several US-based organizations had outlined; these organizations include the American Academy of Pediatrics, the Centers for Disease Control and Prevention, the Clinical Data Interchange Standards Consortium, the Environmental Protection Agency, the International Conference on Harmonisation, and the Systematized Nomenclature of Medicine. The US Food and Drug Administration defines pediatric patients as aged up to 16 years only and uses fewer age categories but with their broader categories coinciding with the categories proposed, which are: neonates, 0 to 1 month; infants, 1 month to 2 years; children, 2 to 12 years; and adolescents, 12 to 16 years.<sup>35</sup>

Here we describe steps toward further investigation of recommended age groups. However, pending the development of additional guidance, we propose the aforementioned integrated guidelines could be used as a basis for establishing age groups and age-based subgroups for RCTs in child health. If future trials use these age groups, data synthesis will be improved and further exploration of age group variation and similarity regarding treatment response and safety will be possible. In addition, recommendations will be able to be tailored to these age groups as 1 step on the pathway to “individualized” medicine or at least “stratified” medicine.

*What If These Age Groups Are Too Broad or Too Narrow?*

The aforementioned age groups are merely proposed as a starting point intended to establish consistency. If

**TABLE 2** Age Stages Defined According to NICHD Pediatric Terminology

Stage	Definitions (Release Date July 6, 2011)
Preterm neonatal	The period at birth when a newborn is born before the full gestational period
Term neonatal	Birth– 27 d
Infancy	28 d–12 mo
Toddler	13 mo–2 y
Early childhood	2–5 y
Middle childhood	6–11 y
Early adolescence	12–18 y
Late adolescence	19–21 y

NICHD, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

trialists feel that any age group is too broad for a study of a particular intervention, it is reasonable to use further division within the proposed subgroups for analyses as appropriate for a particular subspecialty, trial topic, and/or intervention. This division should be justified, and it should be described whether it was decided a priori or was proposed after additional exploratory post hoc analyses. Conversely, in many trials, it may be totally justified to include a broad age range, including  $\geq 2$  of the noted age categories. Even then, it would be useful, however, to present information for each of the included age subgroups.

### What If Other Predictors of Outcome Are Known or Likely?

As outlined here, the use of age-based groups is simply a proxy marker for biological, developmental, psychological, and social changes that occur during the process of maturation from birth to adulthood. For any given intervention, it is likely that there are many likely predictors of outcome; therefore, it is appropriate to assess these in conjunction with different age groups included in the study to describe the interaction of age and other important factors. This is in keeping with a recommendation by the US Food and Drug administration that states “If a sponsor bases its studies on characteristics other than ages, such as physiological development, the sponsor should support its categories with scientific, developmental, compliance, or ethical reasons.”<sup>36</sup> The essential point here is that if the broad age-based subgroups are adhered to, we will be 1 step closer to consistent reporting and more able to explore these other important predictors of outcome. As for the age groups, it should also be described for other factors whether their selection, handling (eg, categorization for continuous

variables), and analysis plans were decided a priori or explored post hoc.

## RESEARCH AGENDA

Further research is needed to establish evidence for the importance of age groups in trial design and the optimal age groups for child health research. Our research agenda is outlined in Table 3.

We plan 2 steps of further exploration to consider if the integrated recommended age groups should be adopted as an international framework for age group allocation. First, we will supplement the information now available from the United States by searching for existing guidance from agencies from other countries and international bodies to build on the synthesis of evidence gathered to date. We will also access literature regarding biological, developmental, physiologic, and social development and reported age ranges. Second, we plan to embark on a Delphi process with the goal of eliciting expert opinion about the best age groups given the

international literature gathered in our first activity.<sup>37,38</sup> Delphi processes have been used for identifying research priorities/agendas,<sup>39</sup> establishing consensus for standards/validation of standards,<sup>40</sup> and selecting health care quality indicators.<sup>41</sup>

The utility of the schema for considering the likely impact of age group differences on trial design will also be assessed and whether these systems and methodologic differences are a good framework for making decision about age groups to be considered in the design and analysis of trials.

Furthermore, we will continue to explore whether differences in effect sizes are observed for these different age groups based on published trials and systematic reviews. We will also catalog validated multivariate predictive models of treatment outcome interactions. We also plan to explore the impact of consistent age groups for data synthesis in pediatric topics. Once guidelines are adopted and implemented, the entire pediatric research community

**TABLE 3** Research Agenda

Aim	Methods
<ul style="list-style-type: none"> <li>• Gather existing age group guidance</li> <li>• Seek consensus</li> <li>• Assess the utility of our suggested schema for considering the likely impact of age group differences on trial design</li> <li>• Explore the effect of age groups on outcome for a range of conditions and interventions</li> <li>• Assess the impact of consistent age groups for data synthesis in pediatric topics</li> <li>• Catalog and update validated predictive models for treatment outcome interactions</li> </ul>	<ul style="list-style-type: none"> <li>• From national and international agencies, as well as from literature about biological, developmental, psychological, and social changes with age</li> <li>• Use a Delphi process to reach consensus about suitable age groups to be adopted for international use if pediatric trials</li> <li>• Recruit trialists to use the schema and report on its ease of use and whether it influenced decision-making about age groups for their planned trial</li> <li>• We will explore the presence, prevalence, and magnitude of age-treatment effect interactions in a large number of clinical conditions and interventions</li> <li>• We will review pediatric systematic reviews that currently exist and quantify the extent to which inconsistent age groups have contributed to an inability to synthesize data or develop clinically meaningful recommendations</li> <li>• Catalog and keep updated appraisals of the evidence regarding multivariate predictive models for treatment outcome interactions that have been well validated and have adequate discriminatory performance that may improve the design and analysis of clinical trials</li> </ul>

will be able to contribute to our knowledge of whether these age groups are useful by reporting treatment effect differences based on age groups and other factors linked to outcome, and by reporting if data synthesis for clinically meaningful age groups is possible and informative.

At the same time, it should be recognized that consideration of age alone may not be sufficient to provide meaningful information about observed effect differences for many clinical conditions and outcomes. For some, multivariate predictive models may be available that have been well validated and have adequate discriminatory performance.<sup>25</sup> Such models should be considered for risk stratification and risk–treatment interaction assessments. Future research could try to catalog and keep updated appraisals of the evidence on such informative, validated, and easy-to-use models that may improve the design and analysis of clinical trials as they emerge.

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**TABLE 4** Recommendations for Practice

- Consider the use of appropriate age range in the eligibility criteria, age-related stratification, and age-related analysis plans during the design phase of every pediatric trial
- Consider the use of age groupings outlined by the Eunice Kennedy Shriver National Institute of Child Health and Human Development
  - Use smaller or wider age ranges when appropriate and justify reasons for doing so
  - Detail whether use of smaller or wider age ranges was decided a priori
- Ensure biological, developmental, psychological, and social variables are appropriate for trial design for included ages
- Consider use of full well-validated and well-performing multivariate predictive models for risk stratification and evaluation of risk–treatment interactions in conditions for which these exist
- If individual patient data are available for systematic reviews, then the tailoring of age group–based analysis for optimal assessment of ideal age groups, interactions with other factors, and age–treatment interactions may be possible

## CONCLUSIONS

Our recommendations for practice are summarized in Table 4. Adopting consistent age groups for use in pediatric trials today may lead to benefits in terms of data synthesis and intertrial comparison. It is likely to also improve the type of information that is available to clinicians, parents, service providers, and policy makers regarding treatment effectiveness and safety by providing that information for clinically meaningful age groups in which high-level variability of effect size is not

anticipated. Moreover, it will provide opportunities to further refine and improve our knowledge of the legitimacy of age groups in existing guidance by providing the crucial skeleton on which research examining specific differences between and within age groups for additional informative markers can be completed.

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