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Data Analysis in Pediatric Clinical Trials

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ABSTRACT

Pediatric clinical trials are the cornerstone of developing effective and safe medical interventions for children. Unlike adults, pediatric patients have unique physiological and developmental characteristics that necessitate a specialized data collection and analysis approach in clinical research. The paper outlines the critical characteristics of pediatric data, including age cohort stratification, the distinct nature of adverse events, and the implications of missing data. It highlights the necessity of using age-appropriate scales and methods for analyzing safety and efficacy data and emphasizes the importance of accurate age accounting in analyses. Additionally, the paper addresses the complexities of pharmacokinetics in pediatric populations, where dosing cannot be directly extrapolated from adult studies. By providing insights into these unique aspects and discussing various analytical methodologies, the paper aims to enhance the understanding of pediatric clinical data analysis and reporting, ultimately contributing to the development of effective interventions for children.

INTRODUCTION

Pediatric patients are not simply smaller versions of adults. There are fundamental differences between pediatric and adult populations, including the developmental state of target tissues, organs, and systems, the distinct characteristics of the pediatric immune system, and differing dose-response relationships. Due to these unique aspects of pediatrics, as well as safety concerns and strict ethical requirements, findings from adult studies can hardly be directly extrapolated to children. To develop tailored interventions for pediatric patients, dedicated pediatric clinical studies are essential.

However, pediatric clinical trials present unique challenges, including pediatric ethical issues, vulnerabilities of the study population, limited number of children available for participation in a study, difficulty in developing age-appropriate endpoints, limited availability of validated patient-reported outcome measurements, and the potential need to use surrogate endpoints and alternative study designs. These challenges require meticulous planning and careful consideration throughout the study design, trial execution, data collection, analysis, and reporting phases.

As a statistical programmer who has supported several pediatric clinical studies, I have identified unique aspects that should be considered in data analysis. This paper aims to summarize the distinctive characteristics of clinical data in pediatric studies and to highlight critical considerations from a data analysis and reporting perspective.

AGE COHORTS

DATA CHARACTERISTICS

In pediatric studies, participants are typically enrolled by age cohorts. This stratification is essential because each group has unique physiological and developmental characteristics that can affect drug absorption, metabolism, and response. Per ICH E11, any classification of the pediatric population into age categories is arbitrary. Below is a general classification that is suggested in ICH E11[1]. In some pharmacokinetic studies, if the clearance pathways of a medicinal product are well established and the ontogeny of the pathways understood, age categories may be chosen based on any “break point” where clearance is likely to change significantly. It is not obligatory to include all the age cohorts in one study, as waivers and deferrals from regulatory authorities are possible in some specific age cohorts when scientifically justified.

- Preterm newborn infants.
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on region))

Typically, study enrollment progresses from the eldest age cohort to the youngest, ensuring safety and tolerability before proceeding to younger cohorts. After completing each or some age cohorts, safety data are typically reviewed by the external Data Monitoring Committee (DMC) to assess if the younger age cohort can be enrolled.

Especially for neonates and infants, due to their high vulnerability and the reluctance of parents to expose newborns to investigational therapies and invasive tests, the sample size for these age cohorts is usually very small. Meanwhile, additional data such as gestational age, weight at birth, and breastfeeding status are often collected, as these variables can significantly impact adverse events and laboratory data.

ANALYSIS CONSIDERATIONS

When analyzing data, it is crucial to stratify by these age groups to identify age-specific effects. Age or age cohort plays a significant role in data analysis and reporting in pediatric studies. Age cohort often serves as a stratification variable in the efficacy and safety analysis model. In some cases, age itself can also serve as a continuous covariate in the efficacy analysis model, in which case, the age unit should be converted to maintain consistency and avoid issues caused by different age units. Meanwhile, subgroup analyses are typically conducted using age cohort as a classification variable.

Below is an example SAS program where the continuous age acts as a covariate variable in the ANOVA model:

```
if upcase(ageu) = 'DAYS' then aage = age/365.24;
else if upcase(ageu) = 'MONTHS' then aage = age/12;
else if upcase(ageu) = 'YEARS' then aage = age;
aageu = 'YEARS';

proc mixed data = lptda.adeff;
  where apatfl = 'Y';
  class trt01pn;
  model aval = trt01pn aage;
run;
```

For neonates and infants, adaptive, sequential, Bayesian, or other designs may be used to minimize sample size. Meanwhile, additional variables such as gestational age, weight at birth, and breastfeeding status are sometimes used as stratification variables and should be considered during analysis.

ADVERSE EVENTS

DATA CHARACTERISTICS

Pediatric participants have significantly different incidence, severity, and types of adverse events compared to adults. The cognitive abilities and physiological responses of pediatric participants vary markedly between toddlers and adolescents, leading to age-specific differences in adverse events. For example, in vaccine studies, adverse events of interest after vaccination may differ between younger and older cohorts. Objective adverse events that can be observed by parents or caregivers, like decreased appetite and somnolence, would be collected for infants because they cannot articulate sensations such as headache or fatigue. For older children or adolescents, attention may be paid to subjective adverse events, as they can describe their discomfort.

ANALYSIS CONSIDERATIONS

Analyses must be sensitive to subtle signs of adverse events and use age-appropriate scales to capture and analyze these events. It is common practice to conduct age-specific analyses, focusing on adverse events pertinent to each age cohort. When analyzing between-treatment differences in the percentage of participants with events, stratified statistical methods are normally used with age cohort as a stratification factor.

Below is an example R function to calculate the between-treatment differences of AE incidence using the stratified Miettinen and Nurminen method. Note, it is just an example and may need to be updated and validated for your specific study case:

```
calculate_stratified_difference <- function(adsl, adae) {
  stratified_data <- adsl %>%
    left_join(adae %>% select(USUBJID, AESPID) %>% distinct(), by =
"USUBJID") %>%
    mutate(has_ae = ifelse(is.na(AESPID), 0, 1)) %>%
    group_by(AGECOHT, TRT01A) %>%
    summarise(
      event = sum(has_ae),
      total = n(),
      .groups = "drop"
    ) %>%
    pivot_wider(
      names_from = TRT01A,
      values_from = c(event, total),
      names_glue = "{.value}_{TRT01A}"
    )

  meta_result <- metabin(
    event_1, total_1, event_2, total_2,
    data = stratified_data,
    studlab = AGECOHT,
    sm = "RD",
    method = "MH"
  )
}
```

AGE-SENSITIVE ANALYSIS

DATA CHARACTERISTICS

Certain safety or efficacy assessment criteria are highly sensitive to age in pediatric studies. Age plays an important role in pediatric studies, and it is often collected from CRF and calculated using the randomization date and birth date. When the two ages do not match, action should be taken to ensure the age is accurate.

ANALYSIS CONSIDERATIONS

In age-sensitive analyses, it is crucial to accurately account for the age of pediatric participants, particularly considering that children grow during the study period.

When age is used in analysis, adult studies typically use collected age or age calculated from the randomization date and birth date. However, this approach is not always appropriate in pediatric studies, especially for very young participants. For example, in analyzing laboratory adverse events that meet predefined limits of change, the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1(Table 1), demonstrates how event severity grades are closely related to age.

Consider a case where a 20-day-old participant was randomized and then treated for seven consecutive days. If a hematology lab test conducted at the end of the treatment period yields a hemoglobin value of 8.5 g/dL, how can we determine the severity of this hemoglobin decrease event? If the participant is

considered 20 days old, the event meets the criteria for a grade 3 event. However, accounting for the participant's actual age of 27 days at the time of testing, the criteria for 22 to 35 days should be applied, making it a grade 2 event. Obviously, the latter is more accurate in this case.

Below are example SAS programs to calculate age and determine the severity of this hemoglobin decrease event. The latter program should be used in this scenario:

```
* Use the collected age (20 days) at randomization, resulting in a grade 3
event;
randdt = input(randdtc, yymmdd10.);
brthdt= input(brthdtc, yymmdd10.);
age = randdt - brthdt;

* Use actual age (27 days) at the time of lab measurement, resulting in a
grade 2 event;
lbdt = input(lbdtc, yymmdd10.);
brthdt= input(brthdtc, yymmdd10.);
age = lbdt - brthdt;
```

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin, Low (g/dL; *mmol/L*) ≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*

Table 1. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1[2]

MISSING DATA

DATA CHARACTERISTICS

Pediatric clinical trials often experience higher rates of missing data compared to adult studies, primarily

due to participant dropouts and challenges in maintaining follow-ups. Common reasons for discontinuation include withdrawal by parents or adverse events. Handling missing data is crucial to avoid biasing study results and to ensure the validity and reliability of findings. Given that pediatric clinical trials often encounter higher rates of missing data compared to adult studies, it is crucial to carefully consider the strategies for addressing missing data during the protocol design phase, as these strategies can significantly impact the required sample size.

ANALYSIS CONSIDERATIONS

Addressing missing data requires careful consideration of the study's objectives and the nature of the missing data. There is no universally applicable method for addressing missing data at specific time points, and different approaches may lead to different results. To avoid concerns over the data-driven selection of methods, the chosen methods are typically pre-specified in the statistical section of the study protocol or statistical analysis plan (SAP).

In general, conservative approaches are usually used to deal with missing data in pediatric trials. This is to ensure the analysis remains robust and the potential for overestimating treatment efficacy is minimized. There are several methods of handling missing data. The choice of method should be driven by the specific objectives of the study and the classifications of missing data. Below are some of them that are widely used in pediatric studies[3]:

For binary variables, the non-responder imputation (NRI) approach is often used as a conservative method for imputing missing data. This approach assumes non-response for all missing data.

Complete Case Analysis is a popular approach in many adult studies. It excludes all participants with missing data on any necessary variables and conducts subsequent statistical analyses using only those participants who had complete data. This approach may not be suitable in pediatric studies as pediatric studies usually have small sample sizes and high rates of missing data. Thus, excluding missing data may cause a loss of some information and lead to bias and a reduction of statistical power. This approach is not recommended as the primary analysis in a confirmatory trial. However, it can be used as a secondary supportive analysis (sensitivity analysis) to illustrate the robustness of conclusions.

Single imputation methods replace a missing datapoint by a single value and analyses are conducted as if all data were observed. One widely used single imputation method is the Last Observation Carried Forward (LOCF). This analysis imputes the last measured value of the endpoint to all subsequent scheduled but missing evaluations. In some situations, LOCF does not produce conservative estimates.

Multiple imputation is designed to fill in missing data under one or more models and to properly reflect uncertainty associated with the “filling in” process. Instead of imputing a single value for each missing observation, a set of values for each missing observation is generated from its predictive distribution.

Below is a summary of these imputation methods.

Imputation Method	Description	Advantages	Disadvantages	Comments
Non-Responder Imputation (NRI)	Assumes non-response for all missing data	Conservative approach	May underestimate the treatment effect	Used for binary variables
Complete Case Analysis	Excludes participants with missing data and uses only complete data for analysis	Popular in exploratory studies	May lead to bias and loss of information	Not recommended as primary analysis
Single Imputation	Replaces missing data with a single value	Simple and widely used	May not produce conservative estimates	Many methods, like LOCF, BOCF, etc.

Imputation Method	Description	Advantages	Disadvantages	Comments
Multiple Imputation	Generates a set of values for each missing observation from its predictive distribution	Reflects uncertainty associated with missing data	More complex and computationally intensive	Suitable when datasets have multiple variables and relationships

Table 2. Missing Data Imputation Methods

If the confirmatory study has non-negligible missing data, sensitivity analyses may be presented as support for the main analysis. When the results of the sensitivity analyses are consistent with the primary analysis and lead to reasonably similar estimates of the treatment effect, this provides some assurance that neither the lost information nor the methods used to handle missing data had an important effect on the overall study conclusions.

PHARMACOKINETICS

DATA CHARACTERISTICS

Well-designed early phase dosing studies and confirmatory pharmacokinetic studies are critical to a successful pediatric development program. This is because in pediatric participants, particularly younger children, dosing is not necessarily predictable based on the experience in adults or adolescents. Definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in whom the medicinal product is likely to be used need to be conducted in the pediatric population.

Pharmacokinetic studies in the pediatric population are generally conducted in patients with the disease. This may lead to higher intersubject variability than studies in normal volunteers, but the data will better reflect clinical use.

ANALYSIS CONSIDERATIONS

Modeling and simulation are normally used to inform dose selection and/or trial design. For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may provide sufficient information for dosage selection. This can be corroborated by sparse sampling in multidose clinical studies. Any nonlinearity in absorption, distribution, and elimination in adults and any difference in duration of effect between single and repeated dosing in adults would need steady-state studies in the pediatric population. All these approaches can be facilitated by knowledge of adult pharmacokinetic parameters.

Dosing recommendations for most medicinal products used in the pediatric population are usually based on milligram (mg)/kilogram (kg) body weight up to a maximum adult dose. While dosing based on mg/square meter body surface area might be preferred, the errors in measuring height or length (particularly in smaller children and infants) and calculation errors of body surface area from weight and height make it an uncommon indicator. For some medications with a narrow therapeutic index, surface-area-guided dosing may be necessary, but extra care should be taken to ensure proper dose calculation.

CONCLUSION

Pediatric studies require meticulous planning and execution, with age-specific considerations at every stage. From a data analysis perspective, attention should be paid to stratification by age cohorts, age-sensitive analysis, addressing missing data, and modeling and simulation in pharmacokinetics studies. By tailoring data collection and analysis methods to these specific requirements, we can achieve reliable and meaningful results, ultimately improving pediatric healthcare outcomes.

REFERENCES

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). “Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population”. 18 August 2017. Available at https://www.ich.org/page/efficacy-guidelines

[2] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. “Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1”. July 2017. Available at https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

[3] European Medicines Agency. “Guideline on missing data in confirmatory clinical trials”. 20 September 2010. Available at Missing data in confirmatory clinical trials - Scientific guideline | European Medicines Agency (EMA)

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