Paper DS05

Empowering Pediatric Drug Development: CDISC standards and ICH guidelines for Clinical Trials with Little Participants

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ABSTRACT

The development of safe and effective medicinal products for pediatric population requires careful attention to ethical, scientific, and practical considerations. The ICH E11 and Clinical Data Interchange Standards Consortium (CDISC) Pediatric User Guide have had a profound impact in the field of pediatric drug development. ICH E11 emphasizes the importance of considering the unique physiological and developmental characteristics of little participants in clinical trial design and provides specific guidance on endpoints, dosing, safety assessment, and ethical considerations. Also, the recently published CDISC Pediatric User Guide provides a standardized approach to data collection, analysis, and submission in the pediatric population, emphasizing the importance of data standardization and quality control. As statisticians and statistical programmers, it is essential that we adhere to these guidelines to optimize the development of pediatric drugs. By integrating the principles outlined in ICH E11 and the CDISC Pediatric User Guide and following standardized statistical programming practices and guidelines we will ensure that statistical analyses are accurate and reproducible and help to minimize errors in the data analysis process. In this paper, we explore the key considerations outlined in the ICH E11 and CDISC Pediatric User Guide, and how they can be leveraged to optimize the development of pediatric drugs.

INTRODUCTION

Children are not little adults*;* they require treatments that have been particularly designed for them. Their bodies are still developing, and it's distinct in physiological development, metabolism, and susceptibility to various ailments. What proves efficacious or benign for adults may bear entirely different consequences when administered to pediatric participants. Thus, pediatric clinical trials represent a cornerstone of modern healthcare, serving as a critical vehicle for the advancement of medical knowledge and the enhancement of healthcare outcomes for the most vulnerable among us—newborns, infants, children, and adolescents. They are essential for developing the creation of the appropriate dose or formulation of a drug for a kid. So, in simple terms, little participant's participation in clinical trials assists us in developing medications that are both safe and effective for pediatric population.

Pediatric drug development has undergone significant changes in recent years, driven by a growing recognition of the need to improve pediatric population's access to safe and effective medications. Before the establishment of pediatric regulations, pediatric healthcare faced challenges due to limited pediatric-specific drug development. This resulted in off-label drug use and instances where potentially beneficial medications were not approved for pediatric populations. However, regulatory agencies in the United States (US) and the European Union (EU) recognized the urgency to address this issue, leading to significant changes. The introduction of the Pediatric Research Equity Act (PREA) in 2003 made it mandatory to include pediatric populations in drug development studies. Based on learnings from PREA, the EU introduced the Pediatric Regulation (Regulation (EC) 1901/2006) in 2006 and combined mandatory requirements with rewards and incentives to promote pediatric drug development.

Additionally, international harmonization efforts, such as ICH E11 and ICH S11, provided guidelines for clinical and non-clinical investigations in the pediatric population. Notably, the CDISC has recently published data standards user guide for pediatric clinical trials which focuses on cross-cutting clinical concepts related to pediatric research to facilitate data exchange and improve the consistency and quality of data collected in pediatric clinical trials. The overarching objective of all these efforts is to ensure that pediatric population have access to medications that have undergone thorough evaluation and are appropriate for their respective age and/or weight categories.

The transformation of pediatric drug development from off-label use to a structured and regulated process has significantly improved their access to appropriate medications. Regulatory initiatives in the US and the EU, along with international harmonization efforts, have paved the way for a more comprehensive and thoughtful approach to pediatric drug development. This evolution represents a crucial step toward enhancing pediatric healthcare and ensuring that they receive the care and treatment they deserve.

NAVIGATING THROGH REGULATORY REQUIREMENTS: PIP & PSP

Pediatric Investigation Plan (PIP): A Pediatric Investigation Plan (PIP) is a regulatory requirement in the EU for pharmaceutical companies developing medicinal products for pediatric population and is typically submitted early in the drug development process, often during the initial phases of clinical development before marketing authorization application.

Scope: PIPs are required for new drugs, biological products, or changes to existing products, including new indications, new route of administration and formulations, that are under development for diseases that also affect pediatric population.

Components: A PIP includes details on the proposed pediatric studies, timelines, and measures to adapt the drug's formulation and dosing to suit different age groups within the pediatric population. The plan must be agreed upon by the European Medicines Agency (EMA) before marketing authorization.

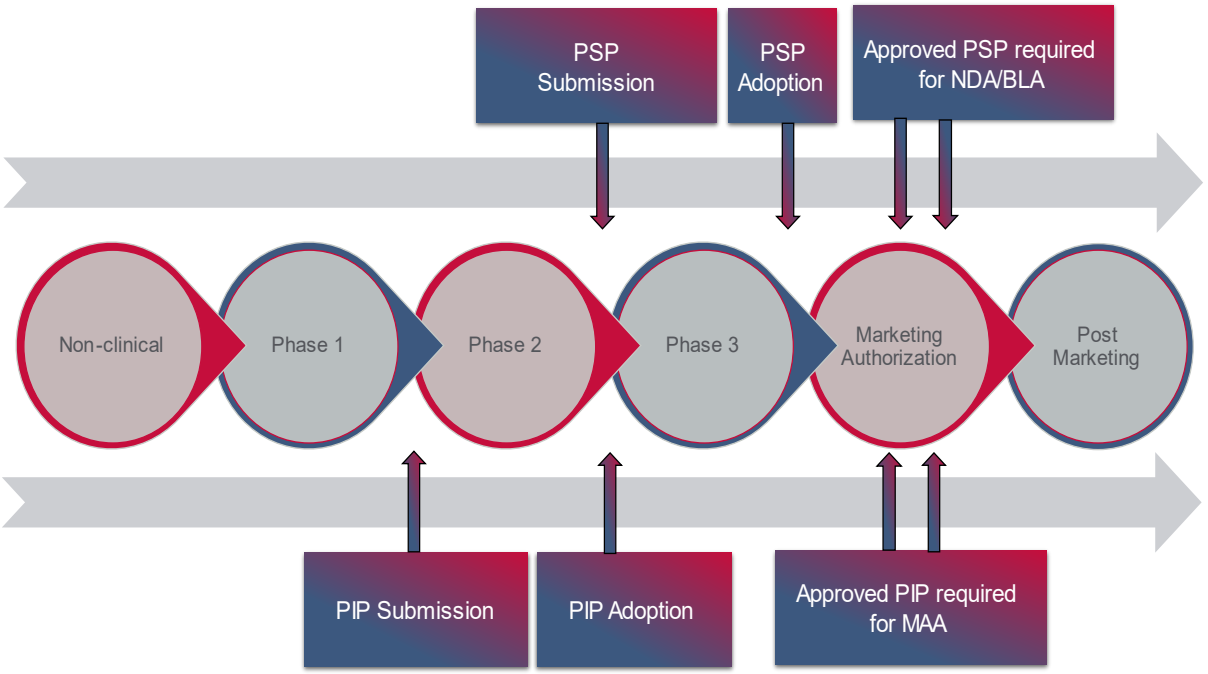
Enforcement: Failure to comply with a PIP can result in regulatory consequences, such as delaying marketing approval or potential financial penalties

Pediatric Study Plan (PSP): Pediatric Study Plan (PSP) is a similar requirement in the United States regulated by the US FDA. PSP is required later in the development process, typically when a drug is already in the approval pipeline to ensures that pediatric medications undergo rigorous testing to establish their safety and efficacy.

Scope: PSPs are typically required for drugs and biological products if sponsor is planning to submit a marketing application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration for the pediatric population.

Components: PSP outlines the pediatric studies that the sponsor plans to conduct, along with their timelines and details. The plan is submitted to the U.S. Food and Drug Administration (FDA) as part of the drug approval process.

Enforcement: Non-compliance with PREA requirements can lead to regulatory consequences, such as delayed approval of the drug or the imposition of post-marketing pediatric study requirements.



In summary, both PIP and PSP serve the common goal of promoting pediatric drug development and safety, while they are specific to their respective regulatory regions (EU and US) and have slight differences in scope, timing, and compliance.

IMPORTANCE OF HARMONIZATION/STANDARDIZATION & ROLE OF GUIDELINES

Harmonization in clinical trials is fundamental to ensuring the integrity, reliability, and efficiency of research endeavors. It involves the use of consistent data collection methods, terminology, and processes across trials, aligning practices across stakeholders and jurisdictions. The impact of these practices on pediatric drug development and healthcare is multifaceted. It also enables robust evaluations of safety and efficacy in pediatric populations with standardizations which enhance data quality and integrity.

Regulatory authorities, including the FDA and EMA, rely on standardized data to assess new medicinal products, expediting approvals and ensuring that pediatric population have access to safe and effective treatments. Moreover, these practices enable cross-trial comparisons, critical in pediatric research, where participant populations are limited. As a result, harmonization not only reduces development costs but also accelerates the drug development process, benefiting both researchers and participants. Furthermore, this aligns with principles of transparency, accountability, and participant protection which are paramount in any clinical trials. Ultimately, the global adoption of standardized and harmonized approaches in pediatric clinical trials fosters international collaboration, bringing us closer to addressing the unique healthcare needs of pediatric population on a global scale and improving pediatric healthcare outcomes.

ICH E11, titled "Clinical Investigation of Medicinal Products in the Pediatric Population," provides comprehensive guidance for the design, conduct, and evaluation of clinical trials involving pediatric participants. The guideline is organized into several sections, each addressing key aspects of pediatric clinical trials. Here are the main contents of ICH E11:

Clinical Data Interchange Standards Consortium fosters the development of data standards for the collection, analysis, and submission of clinical research data to regulatory authorities. Very recently, CDISC, in partnership with conect4children (c4c), has released the **Pediatrics User Guide (TAUG)**. As with all CDISC standards, the primary objective of this guideline is to elaborate the utilization of CDISC standards for the representation of data relevant to pediatric research. It further extends the scope of foundational standards to encompass data related to pediatric clinical trials, encompassing disease-specific metadata, illustrative examples, and comprehensive guidance on the integration of CDISC standards for diverse purposes.

It is a Herculean task to summarize all recommendations from the Pediatrics User Guide, however below are the critical guidelines which will be helpful for further standard implementation.

Age and Age Units: In pediatric studies, we sometimes need to gather participant's age using units other than years. When we do collect age in years, we typically round it down to the nearest whole year. However, if we're using units other than years, we often need to collect precise ages without rounding. Gathering precise age data is essential when assessing the growth and development of newborns and infants. For this purpose, it's crucial to collect or calculate gestation age, postmenstrual age, and postnatal age as well.

Informed consent and Informed Assent: In pediatric studies, informed consent is typically obtained from the participant's parent(s), legal guardian, or other legally authorized representative (LAR). However, in cases where local laws define emancipated or mature minors, participants may be able to provide autonomous consent. The obtaining of informed consent is also represented in the Disposition (DS) domain as a protocol milestone (DSCAT = "PROTOCOL MILESTONE") and date of the initial informed consent is recorded in the RFICDTC variable in the Demographics (DM) domain. Informed assent may be required from the participants depending on their age and is similarly represented in the DS domain. If the participant's LAR or the participant themselves withdraws consent or assent, this event is recorded in the DS domain as a reason for non-completion of the study (DSCAT = "DISPOSITION EVENT").

Body Measurements: In pediatric studies, body measurements serve various purposes, including assessing general health, physical development, severity of medical conditions and determination of other study procedures (e.g., dosing based on body weight or body surface area [BSA]). These measurements, such as height or body length, weight, body mass index (BMI), BSA and head, waist, and mid-upper arm circumference, are captured in the Vital Signs (VS) domain. It's important to note that vital signs, including body measurements and body function tests, can change as they grow. To make meaningful comparisons in pediatric studies, the collected results should be compared to the expected values based on the normal growth pattern of pediatric population from a similar population group. This comparison is typically expressed as either a percentile or a z score, indicating how the observed result differs from the mean value for the population. Best practice dictates that only the results of vital signs tests should be collected, with representation solely in the VS domain and percentiles or z scores should be derived programmatically during analysis and represented exclusively in analysis datasets.

Reproductive Development: Information on reproductive development is frequently gathered in pediatric studies since it may be impacted by the condition being studied or its therapies. Reproductive development can be evaluated using established methods like the Tanner scale. Alternatively, it can involve the collection and reporting of significant developmental milestones (e.g., the onset of menstruation) or specific assessments of reproductive development (e.g., measuring testicular volume). The Tanner scale is a tool used to evaluate external physical development in both males and females. In males, these characteristics encompass the development of genitalia (such as the scrotum, testes, and penis) and the growth of pubic hair. In females, it involves assessing breast development and the development of pubic hair. The Tanner staging system categorizes each of these aspects of development into one of five stages for the participants ≥ 6 years of age.

Family Background: In pediatric studies, data may be collected about the participant's family as well. Details of medications taken by members of the participant's family may be collected in pediatric trials for several reasons. For example, medications taken by a participant's mother while pregnant or breastfeeding may be of interest, as these medications may be transferred to the participant. Similarly, medications taken by the participant's s father before or at the time of conception might be of interest, as these might influence the participant's development and this data will be mapped to associated persons domains (here in this case **AP**CM).

Questionnaires, Ratings, and Scales (QRS): Pediatrics studies may use different QRS instruments which assess symptoms or a particular symptom, such as functional status (i.e., ability to perform functions of daily living) or health-related quality of life. Examples of QRS that may be of interest in pediatric studies include acceptability and palatability of the drug, evaluation of the participant's level of consciousness; specific assessment of reflexes; and the Apgar score, which is commonly used in neonatal studies as a surrogate measure of neurological function.

CONCLUSION

In conclusion, the development of safe and effective medicinal products for pediatric populations requires a comprehensive approach that aligns with ethical, scientific, and practical considerations. ICH E11 and the CDISC Pediatric User Guide offer indispensable guidance and standards that facilitate the optimization of pediatric drug development. By integrating these principles into clinical trial design, data collection, analysis, and submission processes, we can work towards ensuring that pediatric drug development is not only efficient but also leads to improved healthcare outcomes for little participants worldwide. This will enable accelerating approvals, fostering cross-trial comparisons, reducing costs, and promoting international collaboration.

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