ICH E11A: Pediatric Extrapolation

Step 4

Step 4 document – to be implemented
21 August 2024

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

2

Background

- **This document has been signed off as *Step 4* document 21 August 2024 to be implemented by the ICH Regulatory Members**
- **This document was developed based on a Concept Paper (17 October 2017) and Business Plan (17 October 2017)**

Key Principles

- **Development of a Pediatric Extrapolation Concept**
- **Development of a Pediatric Extrapolation Plan**
- **Statistical/modeling methods that can be used to support a Pediatric Extrapolation Concept and Plan**
- **Discussion of different study designs and safety considerations in the Pediatric Extrapolation Concept and Plan**
- **Discussion of adolescent patient enrollment in the context of a Pediatric Extrapolation Plan**

Guideline Objectives

- **Provide recommendations for, and promote international harmonization of, the use of pediatric extrapolation to support the development and authorization of pediatric medicines**
- **Address and align terminology related to pediatric extrapolation**
- **Provide information on various approaches that can be utilized to support the use of pediatric extrapolation**
- **Discuss a systematic approach on the use of pediatric extrapolation**
- **Discuss study designs, statistical analysis, modeling and simulation analyses and respective methods**

Table of Contents

Table of Contents (cont.)

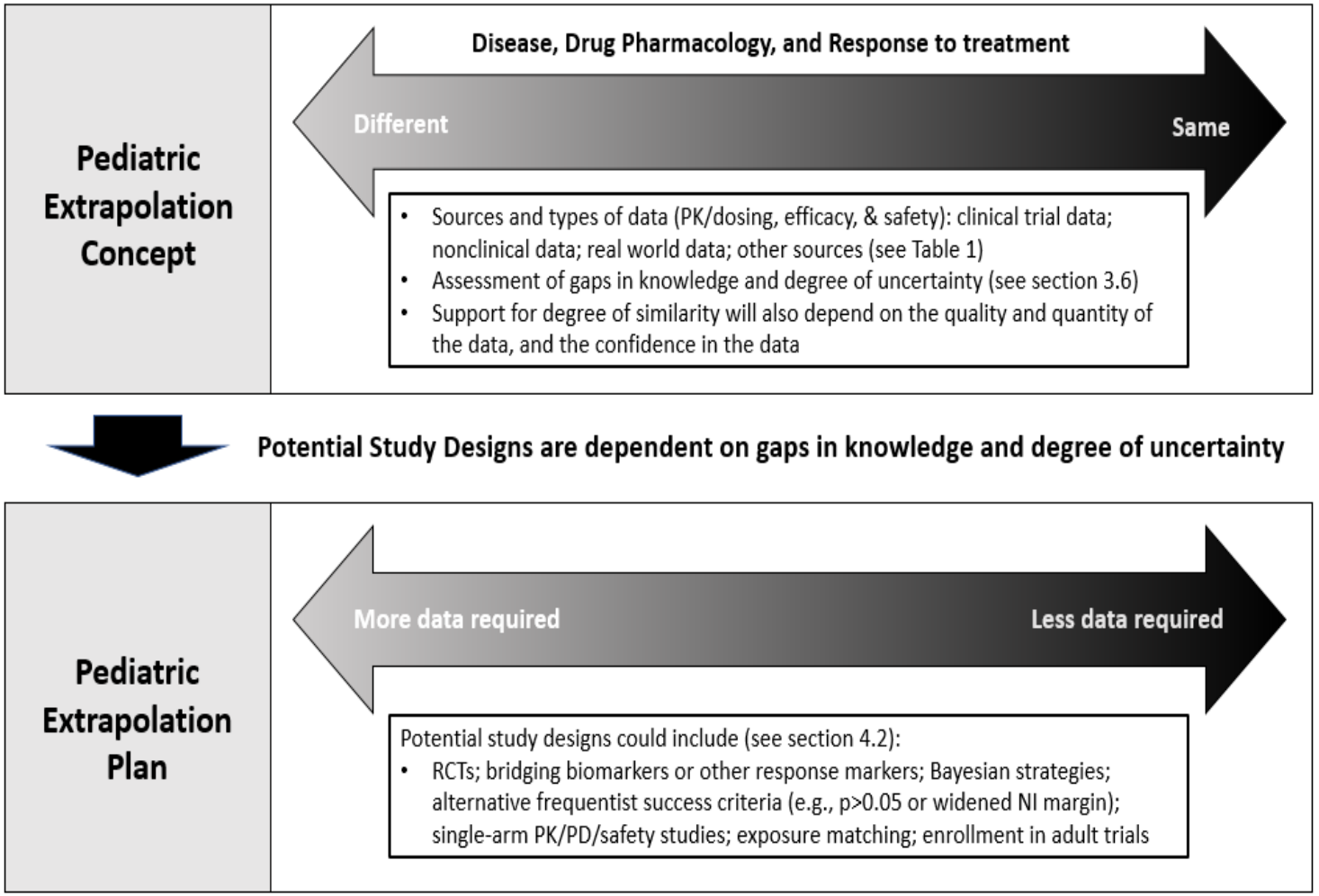
Summary of Guideline Content

Pediatric Extrapolation Introduction and Framework

- Provides overarching description of the three parts of the Pediatric Extrapolation Framework
  - Development of the Extrapolation Concept
  - Creation of the Extrapolation Plan
  - Execution of the Extrapolation Plan
- Provides detailed expansion of the relevant information as outlined in the ICH E11(R1) Guideline
- Distinguishes the use of pediatric extrapolation from other types of extrapolation used in drug development

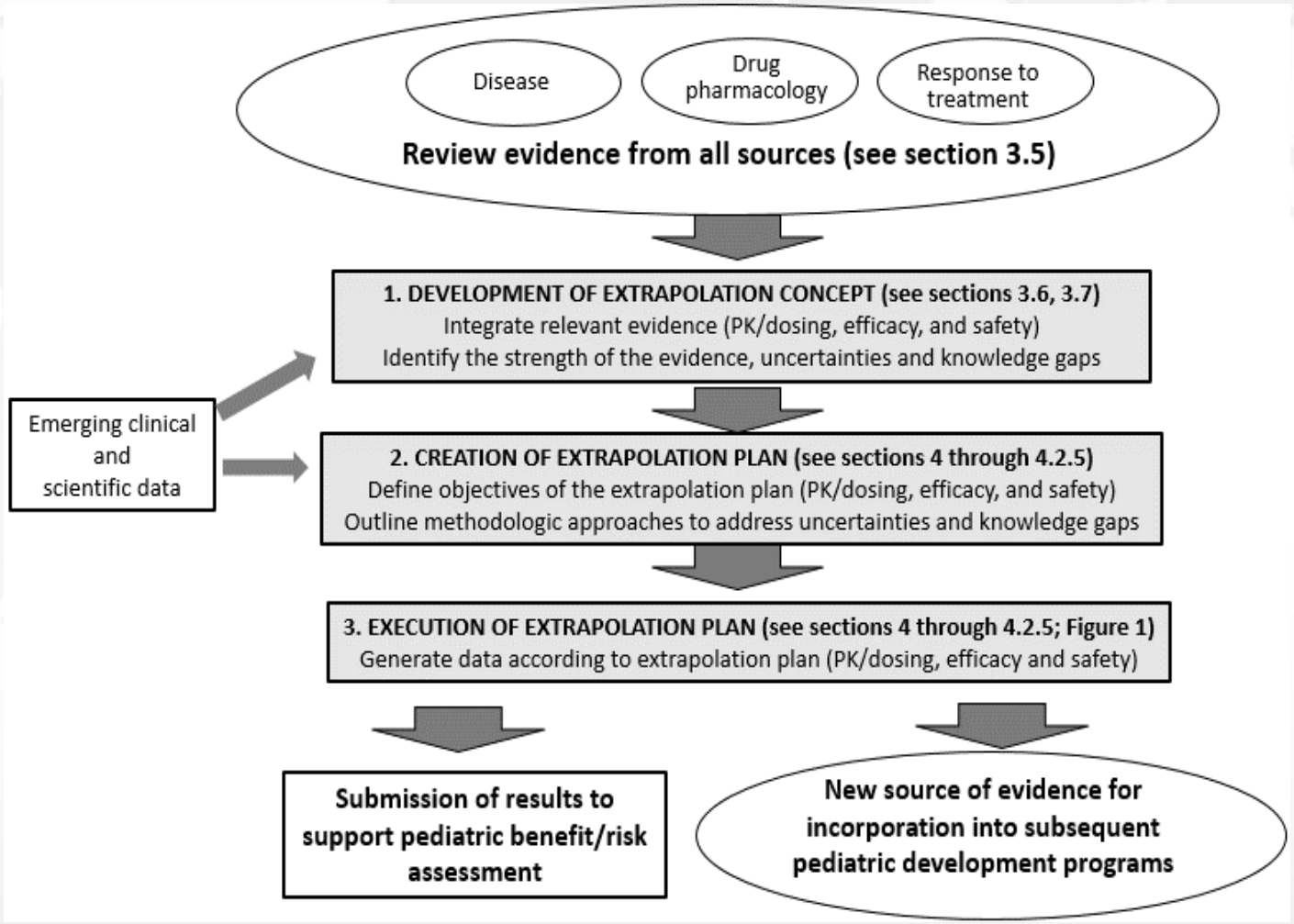
ICH E11A Pediatric Extrapolation *Step 4*

Figure 1: Pediatric Extrapolation as a Continuum



ICH E11A Pediatric Extrapolation *Step 4*

Figure 2: Pediatric Extrapolation Framework



Summary of Guideline Content

- **Pediatric Extrapolation Concept**

  This section:

  - Provides discussion of the factors, including a list of key questions that should be asked, in evaluating the data used to support similarity of disease, drug pharmacology, and response to treatment
  - Puts forth considerations for extrapolation of safety as part of the Pediatric Extrapolation Concept, including key questions that should be asked
  - Describes the sources and types of existing data that should be evaluated in developing the extrapolation concept
  - Explains how the data reviewed can be integrated to finalize a Pediatric Extrapolation Concept
    - Identification of knowledge gaps that need to be addressed as part of the Pediatric Extrapolation Plan
    - Overview of how the Pediatric Extrapolation Concept should be presented

Summary of Guideline Content

- **Pediatric Extrapolation Plan**

  This section:

  - Provides important general considerations in the development of a Pediatric Extrapolation Plan, including inclusion of adolescents in adult trials; use of modeling and simulation approaches, dose selection; use of dose ranging data; use of biomarkers; establishing relationships to different endpoints between a reference and target population; and development of the safety extrapolation plan
  - Discusses study design approaches that can be used as part of a Pediatric Extrapolation Plan based on the gaps in knowledge and uncertainties that have been identified in the finalized pediatric extrapolation concept

Results of Public Consultation

- **There were approximately 1200 comments received during the public consultation. The EWG reviewed every comment received.**
- **There were no major changes to the content of the guideline. However, numerous revisions were made to provide greater granularity and clarity of the content**
- **Additionally, the following structural changes to the document were made:**
  - Figures 1 and 2 were updated
  - Many sections were moved, and section titles were changed to improve flow and clarity of the guideline

Guidelines for Implementation

- **It is expected that this guideline will be implemented in all ICH member regions.**
- **It is not expected that there will be major exceptions in the implementation of this guideline.**
- **Based on the available data at any given time, there may be differences in how pediatric extrapolation is used. This guideline can aid sponsors and regulators as individual plans are discussed.**

Considerations

- **There is a need to incorporate multidisciplinary expertise in the development of a pediatric extrapolation concept and plan (e.g., clinical, clinical pharmacology, biostatistics)**
- **Development of a pediatric extrapolation concept and plan should start early in adult drug development in order to obtain data that can support the concept and approach**
- **It is recommended that sponsors discuss the acceptability of the proposed approach with regulatory authorities, as appropriate (depending upon the region)**
- **Other guidelines relevant to pediatric extrapolation (e.g., ICH E11, ICH E11(R1), E2, E5, E6, E17, E9, E9(R1), E19) are referred to in the E11A Guideline**

Conclusions

- **This Guideline is intended to provide important considerations regarding the development of a pediatric extrapolation approach to assist drug developers and regulators in the development of medicines for pediatric patients.**
- **Additional training materials will be developed to complement the Guideline**

Contact

- **For any questions please contact the ICH Secretariat:**

admin@ich.org