EMA
EUROPEAN MEDICINES AGENCY

External controls in Paediatric Investigation Plans (PIPs)

Workshop on use of external controls

3rd of November 2025

Specific use cases I

Therapeutic area – metabolic disease

- Gene therapy targeting ultra rare X-linked genetic disorder affecting cardiac, skeletal, and neurological function – presenting with cardiomyopathy, skeletal myopathy, and intellectual disability.
- Only symptomatic treatment available for cardiac manifestations – male life expectancy average of 19 years, facing sudden death from arrhythmia or heart failure.
- No specific therapy available.

Clinical development for ATMP - disease modifier

- Single arm trial agreed to by EMA's Paediatric Committee (PDCO), with retrospective and prospective patient data collection to describe the natural history of the disease.

Specific use cases II

Therapeutic area – oncology

- Patients with relapsed/ refractory mature B-cell malignancies; ultra rare disease (around 30 patients per year globally).

Clinical development – in context of a platform trial*

- EMA/PDCO agreed to developments (PIPs**) using an international academic-led multi-centre clinical platform trial designed to evaluate the safety and efficacy of priority novel medicines, alone or in combination with existing therapies.
- Where randomisation is not feasible, considerations given to utilising available data in the same cohort as a historical control arm.

* https://www.ema.europa.eu/en/documents/other/letter-support-global-platform-study-novel-medicines-paediatric-and-adolescent-relapsed-and-refractory-b-cell-non-hodgkin-lymphoma-glo-bnhl-platform_en.pdf
** https://www.ema.europa.eu/en/documents/pip-decision/p-0152-2024-ema-decision-6-may-2024-acceptance-modification-agreed-paediatric-investigation-plan-loncastuximab-tesirine-zynlonta-emea-002665-pip02-20-m01_en.pdf

Experience with External Controls in Paediatric Development

- Use of external control is pre-specified in (many) PIPs across various therapeutic areas; increasingly discussed also in relation to publication of ICHE11A Guideline on use of extrapolation.
- Primary Objective(s)
  - Understanding natural disease history
  - Support comparison to treated patients

Paediatric drug development often takes place in the rare disease space where the EU Paediatric Regulation requires development plans.

  - PIPs as opportunity for guided regulatory development support related to use of external control
  - PIPs often include dependencies for applicants to return to SAWP and/or PDCO to further discuss methodological details

Choice of data sources common challenge.

  - Example: Duchenne Muscular Dystrophy (DMD) triggering an EMA funded real-world data (RWD) study to evaluate the fitness-for-purpose of DMD RWD sources for regulatory decision-making*

*https://catalogues.ema.europa.eu/node/4652/administrative-details

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Thank you

Dominik.Karres@ema.europa.eu

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