RWD-derived external controls in regulatory context

Elina Asikanius

Finnish Medicines Agency
Elina Asikanius
14.6.2024

The contents of this presentation are my personal opinion. My remarks do not necessarily reflect the official view of FIMEA, EMA, or any associated working party or committee.

Scope of session

ICH E10: *An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal control group consisting of patients from the same population assigned to a different treatment*

- External controls in the context of **pivotal clinical trials**
- External control data source: **RWD (focus)**, non-interventional study, clinical trial
- Historical control versus contemporary control
- Hybrid designs (combined internal & external control) are out of scope
- Intended role of external control in regulatory submission: **pivotal evidence (focus)**, supportive evidence, no evidence

External controls as primary source of evidence for pivotal clinical trials

B/R assessment

- Marketing Authorisation is a binary decision
  → Uncertainty can be factored in during the review and reflected e.g. in the EPAR and exclusion of data in SmPC Section 5.1
  → Decision is not based on the p-value of the primary endpoint
- Benefit/Risk assessment considers multiple endpoints
  → RCTs provide comparative data from safety to QoL
- RCTs are not easy and straightforward
  → We know how to assess the uncertainties

External control from RWD in B/R assessment

Many sources for uncertainty, for example:

- Data source and treatment are two identical variables
  - All patients in active arm from clinical trial; all patients in comparator arm from RWD
  - Aim is to estimate effect of treatment
- Data generating mechanisms are fundamentally different
  - How to assess imbalances in patient disposition/intercurrent events?
- Usually, no data in RWD for secondary endpoints and safety
  - Important also for assessing consistency of treatment effect

→ There are tools to assess the uncertainties, but they are “absence of evidence” type rather than “evidence of absence”

Single arm trial vs external control

Why is there more precedence for approvals based on SATs than on externally controlled trials?

- SAT based approvals fulfil certain core elements; most importantly an endpoint that can isolate a drug effect → absolute treatment effect or rather a comparison to known zero response to placebo
  - Approval based on descriptive data rather than hypothesis testing
- External control comparisons estimate a difference between the arms
  - Exchangeability is the most important element
  - Exchangeability is a multifaceted concept from population to clinical practise and from endpoint collection to intercurrent events
  - Most clinical trial endpoints do not single out a drug effect

Take home message

- The bar for evidentiary standards in efficacy for B/R assessment is high
- By definition, an external control from RWD adds uncertainty in decision making as compared to an RCT
  - Treatment effect estimate
  - Totality of evidence, including safety
- This additional uncertainty is rarely scientifically justified because alternative designs with less uncertainty are usually possible

In which settings does an external control rather complement the evidence base than adds uncertainty?

Thank you!