External Control Arm Studies in the Context of Pricing and Reimbursement Assessments – Overview on Guidance and Evaluation in Europe

HTA172

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BACKGROUND

- External control arm (ECA) studies use control patients external to a clinical trial to establish comparative evidence.
- For that purpose, data may potentially be sourced from other historical or current clinical trials or from real-world data such as registries, medical charts, or claims data.[1]
- Potential sources of bias, outcomes measures, confounding, and inclusion and exclusion criteria of patients need to be considered for adequate study selection and method of adjustment.[1]
- The IQWiG, NICE and EMA provide detailed guidance on the conduct and reporting of ECA studies.[2-4]

OBJECTIVES

- The aim of this review is to provide an overview of guidance and evaluation by health technology assessment bodies concerning the conduct and reporting of ECA studies.

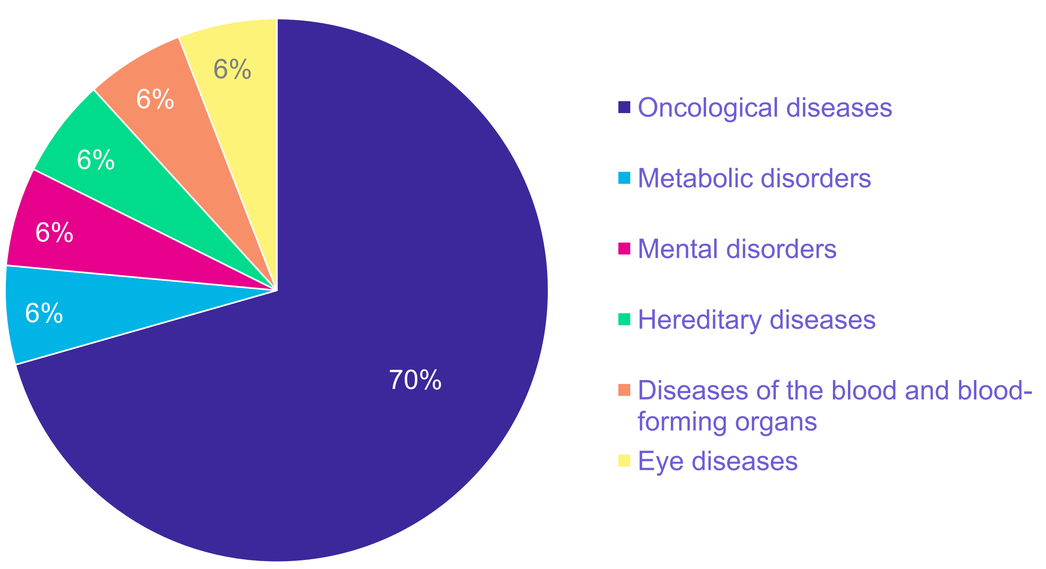
METHODS

- We performed a targeted literature search of guidance for ECA studies with focus on the following institutional documents:
  - German Institute for Quality and Efficiency in Health Care (IQWiG): Rapid report A19-43 Concepts for the generation of real-world data and their evaluation for the purpose of benefit assessment (2020)[2]
  - UK National Institute for Health and Care Excellence (NICE): NICE real-world evidence framework (2022)[3]
  - European Medicines Agency (EMA): Guideline on registry-based studies (2021)[4]
- Furthermore, we screened our internal database of all published German AMNOG benefit dossiers for reported ECA studies and reviewed their evaluation by the IQWiG.
- We included all benefit dossiers with completed assessment status since publication of the IQWiG rapid report on January 24th, 2020 until September 27th, 2022 for investigation.
- The respective module 4 of the benefit dossiers were screened for corresponding keywords and relevant chapters were searched for information on conducted ECA studies.
- To identify key points of criticism stated by the IQWiG and the German Federal Joint Committee (G-BA), the documents of benefit assessment were reviewed.

RESULTS

- The central principles for non-randomized comparisons like ECA studies identified from the considered guidelines of IQWiG, NICE, and EMA are summarized in the following:
  - The explicit replication of the design of comparative studies with randomization is recommended in terms of population, intervention, comparator, outcomes, setting, and time periods (emulation of the target trial).
  - Transparent documentation of the study should be given in a detailed study protocol, analysis plan, and study report.
  - The availability and quality of all relevant data should be ensured and impact from discrepancies should be addressed appropriately.
  - Systematic pre-specification of possible confounders e.g., based on scientific literature with involvement of experts.
  - Approximation of structural equality of the treatment groups by confounder adjustment using individual patient data.
  - When using the propensity score method, positivity, overlap, and balance are important criteria.
  - Pre-planning of sensitivity analyses to test robustness of results.
  - Due to potentially unknown confounders, statements on benefits or harms should only be made from a certain effect size (case-by-case decision depending on quality of data).
  - For orphan diseases, it might be useful to conduct studies in international cooperations.
- The screening of our database resulted in 17 identified benefit dossiers with reported ECA studies.
- This represents about 6% of German benefit dossiers including ECA studies since publication of IQWiG's rapid report on guidance for ECA study implementation.
- Matching-adjusted indirect comparisons (MAIC) and predictor analyses are not recognized as adequate confounder adjustment, which must be performed using individual patient data.
- Therefore, naive comparisons, MAIC, and predictor analyses were not considered for this evaluation.
- Applied adjustment measures in the relevant dossiers of interest with ECA studies were direct matching approach, usage of propensity scores for matching or weighting, and regression.
- Most of the benefit dossiers were in the area of oncological diseases (70.6%), with the therapeutic areas of other dossiers being metabolic disorders, mental disorders, hereditary diseases, diseases of the blood and blood-forming organs, and eye diseases. (**Figure 1**)

Figure 1. Therapeutic areas of the identified benefit dossiers with ECA studies (N=17)



RESULTS (CONTINUED)

- The key points of criticism by the IQWiG related to implemented ECA studies could be structured in 4 major categories with respect to study populations, missing information, methods and data, as well as effect size. (**Table 1**)

Table 1. Key points of criticism by IQWiG identified for ECA study implementation

Adequate control arm and comparability of study populations

• Study populations not sufficiently comparable
  • Eligibility criteria of the studies were not applied concordantly
  • High proportion of patients excluded from the original population for analysis
  • Missing confounders in adjustment without assessment of impact on effect estimates
  • Different observation start times leading to dissimilar disease or treatment status at baseline
  • Different timeliness of studies, so change over time in treatment options/prognosis may bias comparison
  • Insufficient overlap of propensity scores
• Appropriate comparator therapy not realized with control arm

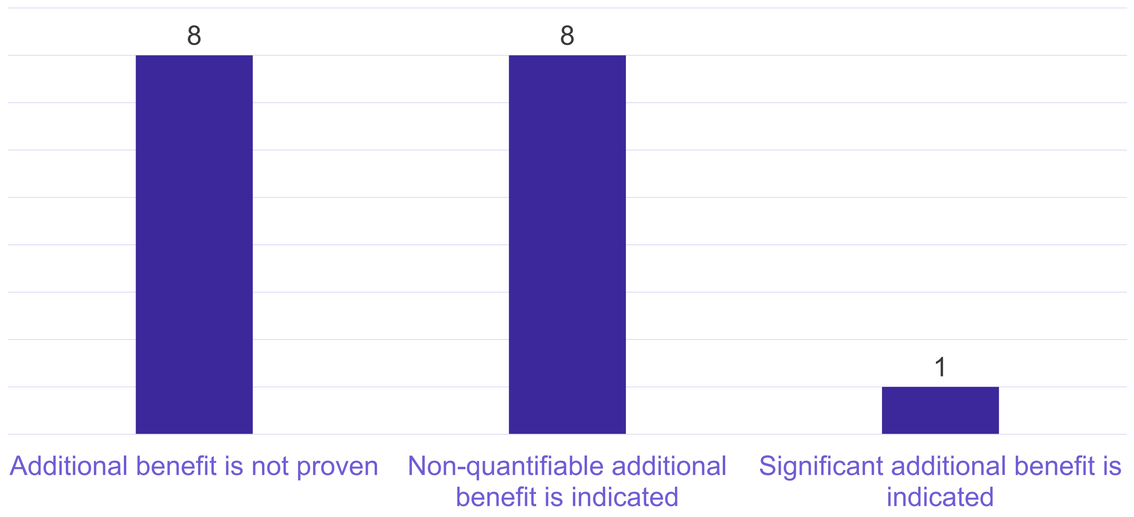
Missing or incomplete information or description

• Protocol of the original study of the control arm not available / Missing description of the original study of the control arm
  • Methodology of data collection unclear
  • Missing description of study center selection
  • Missing description of number of patients screened and reasons for exclusion
  • No information on data quality in terms of accuracy and completeness
  • Missing information on operationalization of endpoints
• Missing SAP for the ECA study
• ECA study not registered in a study registry
• Systematic identification of confounders not described transparently
• Positivity and overlap of propensity scores and balancing after adjustment not shown
• Patient characteristics, composition of agents, and administration according to the SmPC not shown for analysis populations after adjustment

Methodological and data inadequacies
• Poor data quality of the original study of the control arm • Different observation times with rate comparisons only instead of time-to-event analyses • Selective presentation of only part of the relevant/available endpoints (e.g., only benefits without harms) • Selective choice of relevant studies for the control arm without estimation of impact on effect estimate • Systematic identification of confounders not (properly) performed • Inadequate handling of missing values • Outcome driven analysis cannot be excluded as all studies used were completed at the time of SAP finalization
Insufficient effect size
• Effect not large enough that it could not possibly be explained only by systematic bias

- A significant additional benefit was assessed as indicated in 1 of the 17 considered dossiers, and a non-quantifiable additional benefit in another 8 dossiers. (**Figure 2**)
- However, the extent of influence of the ECA studies on the benefit ratings is uncertain.

Figure 2. Extent of added benefit in decision-making on benefit dossiers with ECA studies



CONCLUSIONS

- ECA studies are becoming more commonly accepted in the context of pricing and reimbursement assessments when ethics, orphan diseases, or enrolment challenges limit the conduct of randomized controlled trials.
- Guidance by the IQWiG, NICE and EMA poses similar requirements on the conduct and reporting of such studies.
- Overall, implementation of those requirements needs improvement according to evaluations by the IQWiG.

REFERENCES

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