# Will Health Technology Assessment (HTA) Bodies in Europe Accept Evidence from an External Control Arm to Supplement Evidence from Clinical Trials for Chronic Diseases?

Poster code: PT30

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Insights from payer survey: External Control Arms (ECA) for chronic diseases can be used to enrich the evidence package and its acceptability can be improved by providing a detailed rationale regarding why ECA is relevant for an HTA submission, in combination with the use of appropriate data sources and analytic methods

## Background and Objective

- As Health Technology Assessment (HTA) bodies become more familiar with real-world evidence (RWE), they are increasingly acknowledging its value in complementing clinical evidence, primarily derived from randomised-control trials (RCT).[1]
- External control arms (ECAs) are statistical models that leverage historical or RWE to simulate a control group in a clinical trial[2]. In addition, ECA allows comparison against relevant therapeutic options in case of absence of a comparator as often observed in rare diseases or oncology[2-4].
- However, HTA bodies have highlighted some methodological challenges for ECA studies, such as selection of patients and confounding due to non-randomization, and the evidence on acceptance and relevance of ECA in HTA other than oncology and rare diseases is limited[5-8].
- Therefore, the objective of this study was to specifically investigate opportunities to use ECA to complement the evidence from RCTs in indications outside oncology and rare disease, i.e., in chronic diseases, by using both secondary research and payer interviews.

## Methods

**Secondary research**

HTA guidelines for RWE were reviewed to examine the detail of guidance for ECA analysis, including:
- National Institute for Health and Care Excellence (NICE),
- French National Authority for Health (HAS), and
- Institute for Quality and Efficiency in Health Care (IQWiG)

**Payer interviews**

Furthermore, six double-blinded interviews were conducted with payer experts with knowledge on the use of ECA in HTA submissions in the United Kingdom (UK; n=2), Germany (n=1), France (n=2), and Italy (n=1) to assess the acceptance of ECA. The following topics were discussed:

- ***Use of ECA in HTA****: Discussed the acceptance of ECA in HTA evaluations, specifically when used to supplement data from an RCT*
- ***Drivers of ECA acceptance****: Discussed considerations for designing an ECA study, which can increase the likelihood of acceptance in HTA*

## Key results

- NICE RWE framework provides guidance on ECA, however, insights from HAS* and IQWiG were scarce.[5-8]
- Data suitability, provenance, and transparency are of particular interest for HTA. Data needs to be generalizable to the local context.[6,7]
- Insights from payer interviews indicate that in the UK, NICE is more open to accept evidence that support the findings from RCTs, whereas in Germany there is a stronger preference for RCT alone. In France and Italy there is an increased interest in ECA, but its acceptance remains low (Table 1).
- Acceptance of ECA is higher in the absence of relevant comparator in the RCT, for instance due to evolving treatment landscape or ethical reasons, which are more common in rare diseases or oncology rather than chronic diseases (Table 2).
- Across countries, Indirect Treatment Comparison (ITC) using published RCT evidence is perceived more positively vs ECA, due to a preference of HTA bodies for RCT evidence and familiarity with the methodology. In Italy, ECA with historical RCT data is accepted more than using ECA with RWE data, due to preference for RCT evidence.
- ECA is more likely to be accepted in HTA if a strong rationale supporting its use is provided and if data sources are suitable. Moreover, appropriate methodology should be applied to ensure unbiased analysis, especially when ECA is used for causal inference to estimate relative clinical efficacy.
- At an early stage of study conceptualization, engaging payers via early scientific advice processes is key to increase acceptance of innovative study designs, such as ECA.

**Table 1: Insights from interviews with payer experts on the external control arms acceptance by HTA bodies**

| | 🇫🇷 | 🇩🇪 | 🇮🇹 | 🇬🇧 |
|---|---|---|---|---|
| As a part of the evidence package | | | | |
| To supplement RCT (as opposed to SAT) | | | | |
| In indications outside of oncology or rare diseases | | | | |
| Compared to acceptance of other traditional methods of indirect comparison | | | | |
| Inclusion of justification/rationale for ECA use | | | | |

*Highly accepting* | *Somewhat highly accepting* | *Neutral* | *Largely not accepting* | *Not accepting*

**Table 2: Insights from interviews with payer experts on the situations where external control arm can best contribute to evidence package**

| | 🇫🇷 | 🇩🇪 | 🇮🇹 | 🇬🇧 |
|---|---|---|---|---|
| Missing comparator | | | | |
| Limited data for comparator | | | | |
| Lack of data in the subgroup | | | | |
| Small sample size | | | | |
| Rapidly changing SoC | | | | |
| Inappropriate comparator | | | | |
| Dramatic effect, i.e., deterministic course of the disease | | | | |

*ECA use considered* | *ECA use not accepted* | *Not evaluated*

## Summary

- RCT remains the gold standard in HTA evaluations, however the use of ECA to enrich the evidence package has been increasing despite limited acceptability.
- Acceptance of ECA use in HTA remains low in Italy, France and particularly in Germany, while UK is generally more open to its use.
- ECA acceptance is greatest in case of an absence of relevant comparator as observed in rare disease and oncology or due to ethical reasons.
- ITC using published RCT evidence has higher acceptability compared to ECA with RWE. ECA using historical trial could improve acceptability, as RCT is still considered the gold standard.

## Conclusion

- Recently published guidelines for RWE in HTA provide some guidance for the use of ECA, but additional recommendations would be useful.
- A detailed rationale regarding why ECA is relevant, in combination with the use of appropriate data sources and analytical methods can improve acceptance across therapy areas, ultimately leading to an enriched evidence package (in addition to evidence from RCTs) and reduced uncertainty.
- Thought leadership activities and early and close engagement with the HTA and payers will contribute to shaping perception on ECA in enhancing evidence package of innovative treatments across different therapeutic areas

*Following the completion of this research, HAS updated its methodology[9] on assessing data from uncontrolled trials, stating it is 'open to indirect comparison data of good methodological quality or data from control groups, provided that they are explained and justified by the manufacturer[7]

Abbreviations: ECA, external control arm; RCT, Randomised Controlled Trial; RWE, Real World Evidence; G-BA, Gemensamer Bundesausschuss; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; RCT, Randomized Controlled Trial; SAT, Single Arm Trial; UK, United Kingdom

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**References:**
(**1**) Jaska et al. Front Med (Lausanne). 2022;9:1073678; (**2**) Rippin et al. Drug Saf. 2022;45(8):815-837; (**3**) Proenca. ISPOR EU, Vienna; **(4)** Wogen et al. ISPOR US, 2023, Boston; (**5**) Patel et al. Value Health. 2021;24(8):1118-1125; **(6)** NICE real-world evidence framework, June2022; (**7**) IQWIG, General Methods, Jan 2022; **(8)** HAS, RW studies for the assessment of medicinal products and medical devices, Jun 2021; **(9)** Vanier et al. BMJ Evid Based Med. 2023; 10.1136/bmjebm-2022-112091